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The Journal of Laboratory and Clinical Medicine

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ORIGINAL ARTICLES

THE DIAGNOSIS OF ACIDOSIS*

A REVIEW AND CRITICISM OF THE METHODS AT PRESENT IN USE

BY J. J. R. MACLEOD, M.B., TORONTO, CANADA

THERE has been some confusion in medical literature concerning the exact meaning of the term "acidosis," so that it will be advantageous to preface our discussion of the subject with a brief review of the work upon which the present-day definition is based. The discoveries that large quantities of oxybutyric and oxyacetic acids are excreted in the urine of patients suffering from diabetic coma, and that there is a general similarity between the symptoms of this condition and those which follow the intravenous injection of strong acids (acid intoxication) in laboratory animals, were primarily responsible for the adoption of the term. In seeking earlier signs of acidosis than the actual symptoms of coma, however, examination of the urine for oxybutyric and acetoacetic acids or their oxidation product, acetone, was found to be of uncertain value, since these substances might also appear in decidedly large amounts in the urine of nondiabetic individuals. During starvation, for example, either complete or involving carbohydrate foods alone, acetonuria was frequently met with, which made it clear that the excretion of acetone bodies could not in itself be taken as a reliable indication of impending acidosis.

It was attempted therefore, to develop methods of diagnosis depending, not on the detection of the particular acids, but on the effects which might be produced by the accumulation in the organism of acids in general.

In the first place it was natural to expect that the blood would become

*Delivered before the Medical Section, Academy of Medicine, University of Toronto, Toronto, Canada.

less alkaline as the result of the acid production, and attempts were therefore made to measure the alkalinity of the blood by titrating with standard acid until the point of neutrality was reached, as judged by the change of tint of some indicator. It was hoped that the values obtained by this method would indicate in the blood of cases threatened with acidosis, the presence of more acids than in normal blood; that is, that a smaller amount of standard acid would require to be added to the former, than to the latter blood, in order to cause the tint of some indicator to change. Although with certain modifications this method is theoretically sound, it was found to have little practical value, partly because it requires large amounts of blood, and partly because the coloring matter has to be removed before the test can be applied. Moreover, it came to be recognized that the amount of added acid, with the indicators ordinarily used, would represent, not only the basic constituents that combine with acids in the quantities in which these could be produced in the organism, even under abnormal conditions, but also those, like proteins and phosphates, that might be called upon to functionate as bases when the limits of acidity compatible with life were greatly overstepped.

It became necessary to seek for some other type of reaction which acids might set up in blood, and the well-known effect which these have in expelling carbon dioxide from its combinations with alkalies was investigated (Walter). It was found by experiments on animals that a marked diminution in the CO_2 content of blood was induced by intravenous injections of acids, and the same was observed to be the case in the blood of patients in diabetic coma (Naunyn).[1] In the light of more modern research, by which, as we shall see later, the delicacy and accuracy of this method is fully justified, it is somewhat surprising that it did not receive more extensive application. One serious difficulty stood in the way, namely, the technic of the estimation.

The next step depended on the discoveries of Haldane and Priestley[2] that the percentage of CO_2 in the alveolar air of normal individuals at atmospheric pressure is remarkably constant, and of Krogh that the amount of free CO_2 in the arterial blood is very nearly the same as that in the alveolar air. These facts led Haldane and his collaborators to formulate the hypothesis that the alveolar CO_2 must be proportional to the relative amounts of carbonic and of other (fixed) acids in the blood, and that when the latter are increased there must be a compensatory decrease in the former, provided the control of the respiratory function is normal. The first application of this principle on pathologic acidosis was made by Beddard, Pembrey and Spriggs,[3] who examined the alveolar CO_2 in diabetic patients, with the result that a very pronounced diminution was found whenever the comatous condition existed or was threatened. The rationale of this method and its limitations we shall discuss later; for the present it may be stated that the alveolar CO_2 may also be depressed in other diseases, particularly nephritis, as well as in normal persons whenever acids accumulate in the organism as a result of deficient oxidation in the tissues (Haldane, etc.).

Clearly, therefore, the term acidosis must not be confined to cases of diabetic coma. On the other hand the common appearance of acidosis in this

disease, coupled with the fact that in it the acids are of a type that is different from that found in nephritis, or during partial asphyxiation, makes it important that some term should be set aside to designate the diabetic condition. Since the acids are closely related to ketones (acetones) in chemical structure, the term "ketosis" has been suggested, and is gradually coming into general use. Ketosis, therefore, means the form of acidosis that is caused by the appearance of ketonic acids in the organism. Other forms of acidosis have not as yet been dignified by special names.

The remarkably rapid development of our knowledge of this subject during recent years, coupled with its dependence upon certain fundamental principles of physical chemistry, has made it very difficult for those of the medical profession who have been out of college for several years to appreciate the full significance and value of closely observing the neutrality regulation in the animal body in order that incipient states of acidosis may be detected. I will therefore attempt to review very briefly these fundamental principles, and to explain the various tests by which alterations in the reaction of fluids in general may be detected.

In the first place we must clearly understand what is meant by an acid such as HCl, and an alkali, or base, such as NaOH. When the molecule of either of these chemicals is dissolved in water it splits, or dissociates, into two portions called ions; in the case of HCl, for example, ions of H and Cl are formed, and in the case of NaOH, Na and OH. Moreover, each of the ions carries an electric charge, and this is always of opposite sign for the two ions composing the molecule. The sign of the electric charge for the H ion and all metals is positive, and that of Cl and all acid groups is negative. Since, as is well known, unlike electricities attract each other, this means that the positive ions like H would be attracted towards the negative pole or cathode of a pair of electrical terminals, between which a current is passing, placed in the solution. They are, therefore, called cations, and for the same reason the negative ions are called anions. To indicate these electrical charges, a dot is used for positive, and a dash for negative, thus, H· and Cl′.

But what, it may be asked, have these principles of electrolysis to do with the question of reaction? The answer is that it is the presence of free H·ions that determines the acidity of a solution. If we examine the formula of all known acids it will be seen that they have hydrogen in some displaceable or dissociable form in the molecule, and, furthermore, if we measure the acidity, as judged by the common standards of this property, such as the ability to dissolve metals, the acid taste, the power of inverting sugars and starches, and so forth, we shall find that it runs parallel with the dissociability of the H ion from the rest of the acid molecule. The H·ions present in a free state in the solution must, therefore, be an accurate measure of its acidity. This leads us to expect that the presence of free OH′ ions must be a measure of alkalinity, since we know that when an acid and a base are brought together, the one neutralizes the other by a reaction which consists essentially in the combination H· and OH′ ions to form H_2O. This removes the ions from the free

state and so locks them up, because molecules of water practically do not dissociate.

We have learned two fundamental principles, namely, that the standard of perfect neutrality must be where H· and OH′ ions exactly balance each other, and that the true acidity of a solution will be represented by the excess of free H· ions over OH′ ions, that is, by the H·-ion concentration (C_H). But we can go further, for not only may the acidity be expressed in terms of C_H, but so also may the alkalinity. Why should this be? It is clear that the most strictly neutral solution must be pure water, in which H· and OH′ ions are exactly counterbalanced. Nearly all of the H· and OH′ are combined in an undissociated molecule H_2O, but not all, for even in the purest water a slight degree of dissociation occurs, giving us therefore H· and OH′ ions. When the concentrations of the two ions are multiplied together the product is 1.2×10^{-14}, which means that there are 1.2 gram molecules of hydrogen (or its equivalent) present in, 10,000,000,000,000 liters. Since the concentrations of H· and OH′ ions are equal, the H·ion must therefore, be 1.2×10^{-7}, which means that this ion is present so as to form a .000,000,12 N solution is 1.2 gm. H· in 10,000,000 liters.

When some acid is added to the water the con. of H·ions, of course, rises, but, and this is the fundamental point to bear in mind, the con. of OH′ ions correspondingly falls so that, as in pure water, *the product of the two concentrations is again* 1.2×10^{-14}. However acid or alkaline a solution may be, the product of the concentrations of the H· and OH′ ions is always the same. Clearly then *we may express the reaction even of alkaline solutions in terms of the H ion concentration.* Whenever this is greater than 1.2×10^{-7}, the reaction is acid, but when it is less than 1.2×10^{-7}, the reaction is alkaline.* It is usual to abbreviate the expression hydrogen-ion concentration into C_H.†

These considerations lead us to seek for methods by which C_H may be measured. These are two in number, namely, the electrical and colorimetric. Concerning the former, suffice it to say that it consists in measuring the voltage or electric force set up in a battery of which one electrode is pure hydrogen gas in intimate contact with the solution whose C_H we desire to measure, and the other electrode is one of known voltage, such as the so-called calomel electrode. The rate of diffusion between the free H· ions in the solution and the H which constitutes the one electrode, is naturally dependent upon the concentration of free H· ions, and it is on this that the development of electric force depends at this electrode. Consequently since everything else is constant in the battery, the total electromotive force must be proportional to the C_H of the unknown solution.

The colorimetric method is much simpler, but not so delicate. It depends on the fact that certain indicators change in tint in proportion to C_H. In

*The exact value of 1.2 varies with temperature. When C_H becomes greater than that of neutrality the number 1.2 becomes greater, and if the change be beyond 10 the characteristic (-7) becomes less.

†For convenience of expression it is usual to designate the H-ion concentration by P_H instead of C_H. P_H is obtained by finding the logarithm of the number of gram molecules of H (i.e., 1.2 in the above example), and subtracting this from the characteristic (i.e.,-7 in the above example). Since the minus sign is understood P_H increases in magnitude as the H-ion concentration (expressed by C_H) decreases. In the present article C_H is used because its use is less confusing in a general discussion of the acidosis problem.

titrating solutions, such as the stomach contents, for the degree of acidity, the impression is apt to be formed that the tint changes suddenly at the neutral point. This is not the case however, for if the titration be done by very small additions of acid or alkali about the neutral point, it will be found that there is a fine gradation from the typical acid color to the typical alkaline color.

The exact C_H at which indicators change in tint varies with the indicator. Thus phenolphthalein, which is used in certain titrations of stomach contents, changes in tint at a much lower C_H than methyl orange or litmus, and with none of these indicators does the point of change occur at a C_H of 1.2×10^{-7}, so that they are unsuitable for measurement of the C_H of solutions that are nearly neutral. Fortunately, however, such indicators exist, the best known of which are sulphophenolphthalein, rosolic acid, and neutral red. If therefore we take a series of solutions having slightly variable, but known, C_H about the neutral point, and add to each a drop of one of the latter indicators, we shall obtain a series of graded tints, and the tint will be proportional to the C_H. The preparation of the standard solutions is not a difficult matter, provided ordinary precautions are taken. Mixtures of acid and basic phosphates in varying proportions are most practical.[4] The resulting mixtures should be measured electrometrically for accurate work. In order to determine the C_H of an unknown solution, some of it is placed in a hand glass test tube and an amount of suitable indicator is added so that the proportion of indicator to solution is the same as in the standards. The tint of the standards with which the tint of the unknown matches is then ascertained and this gives C_H. When the colorimetric method is employed for blood, it is of course necessary to get rid of the blood pigment and also of the proteins since these interfere with the reaction. This is accomplished by placing a few cubic centimeters of blood in a dialyser in the shape of a collodion tube, and suspending this in neutral physiologic saline. The saline soon assumes the same C_H as the blood, and this can be measured by the above described method.

When C_H of the blood is measured by one or other of these methods the significant fact is revealed that it is practically always the same, and is not far removed from that of pure water; at 38° C. C_H equals 0.4×10^{-7}. Even in severe cases of diabetic ketosis, an increase in C_H becomes perceptible only in the final stages of the condition. Clearly, therefore, even the slightest increase in C_H is incompatible with life, and C_H of the blood must be considered as a physiologic constant. It is greatly more so than body temperature or blood pressure, so that its measurement can be of little practical value in the clinic, and the question arises as to how the early stages of changes that might ultimately end in death from an increase in C_H may be detected. To answer this question we must study *the nature of the mechanism by which neutrality is maintained in the organism;* in other words why it should be the case that large quantities of acid can be produced in the body, as in diabetes, without any perceptible change in C_H.

When even a trace of acid is added to water or an isotonic solution of sodium chloride, a very pronounced change occurs in C_H, but it requires ever so much more acid to produce any perceptible change in the case of blood. For

example, using the colorimetric method let us observe the change in tint produced by adding a drop of weak HCl to water containing sulphophenolphthalein and then see how much of the same acid must be added to bring about a similar change of tint in a dialysate of blood. It takes very much more. Clearly the blood contains something which as it were soaks up the added H ions. This has been called the *buffer action* of blood, or better still, the *tampon action*. The question is, to what is this buffer action due? A clue is furnished by using solutions of phosphates. For example, if we take a solution containing alkaline and acid phosphates in such proportion that C_H is the same as that of blood, and then add acid, we shall find that ever so much more has to be added than is the case of water. The same is true of solutions of bicarbonate.

This property of phosphate has been carefully studied by L. J. Henderson,[5] to whose brilliant researches we are primarily indebted for the recent development of our knowledge in this whole question. Henderson found that weak acids like acid phosphate and carbonic acid possess the property of holding the H-ion concentration nearly constant, i.e., of acting as buffers, when they are present in solutions containing an excess of their salts. Now, in so far as the blood plasma is concerned, it is not phosphates, but rather bicarbonates to which the buffer action must be due, and as a matter of fact it has been found that C_H is directly proportional to the ratio existing between CO_2 in solution as H_2CO_3 and sodium bicarbonate $NaHCO_3$ multiplied by a constant; or, expressed in chemical notation, C_H = the molecular ratio $\frac{H_2CO_3}{NaHCO_3}$. This ratio is $\frac{1}{20}$, and we may define acidosis as any condition in which the proportion between H_2CO_3 and $NaHCO_3$ becomes greater than 1:20. It must be clearly understood that this applies only to isolated plasma, for when whole blood is used, other substances come into play in maintaining neutrality; the phosphates, for example, though practically absent from plasma, are nevertheless present in the corpuscles through the envelopes of which diffusion more or less readily occurs, so that they serve as a reserve buffer. Proteins also may serve either as weak acids or alkalies, and therefore neutralize quite decided quantities of added acid or alkalies. But for practical purposes we may regard the buffer agency as being the ratio $\frac{H_2CO_3}{NaHCO_3}$ and the problem of finding practical means for the detection of threatened acidosis now narrows itself down to a study of the behavior of this ratio.

Suppose that some fixed acid were added to a buffer solution containing bicarbonate. It would react with $NaHCO_3$ to form a neutral salt of the acid, and consequently set free some H_2CO_3, that is, it would diminish the denominator but increase the numerator of the equation $\frac{1}{20}$. The increase in C_H would not be proportional to that of the added acid, on account of the buffer mechanism (because H_2CO_3 does not dissociate well) but it would nevertheless increase somewhat just as any kind of buffer takes up most, but not all, of a force applied to it. This indicates that if the foreign acid were being added continuously, as would be more or less the case in pathologic acidosis, C_H would rise in spite of the buffer unless some method existed for decreasing the numera-

tor of the equation, i.e., getting rid of H_2CO_3. This is one of the functions of the lungs, the CO_2 excretion through which must therefore, be considered as a necessary part of the neutrality mechanism of the body. The CO_2 is got rid of until the ratio $\frac{H_2CO_3}{NaHCO_3}$ comes back to its old level of $\frac{1}{20}$. But now, much of the $NaHCO_3$ having been used up to combine with the foreign acid, the actual amount present is much less than before. This means that the H_2CO_3 must also be less, that is, the CO_2 in a free state in the blood plasma. Now, since as we have seen, the pulmonary epithelium permits the free CO_2 of the blood to diffuse readily through it, it follows *that the percentage of CO_2 in the alveolar air must be a measure of the available $NaHCO_3$ in the blood.* To repeat, for this is the fundamental conception of the whole acidosis problem, since C_H remains constant in the blood the ratio $\frac{H_2CO_3}{NaHCO_3}$ must also remain at its normal value of $\frac{1}{20}$, and, therefore, if $NaHCO_3$ declines, H_2CO_3 must decline proportionately, and since this diffuses as CO_2 into the alveolar air, the percentage of this gas in the latter must be proportional to the degree to which foreign acid can be added to the blood without perceptibly changing C_H, in other words it must be proportional to the reserve alkalinity.

One other factor must clearly come into play to permit of the smooth operation of the above mechanism, namely, the rate of pulmonary ventilation must be adapted to the amount of CO_2 that has to be eliminated. This adaptation depends on the respiratory center, the activity of which is preeminently dependent upon the acid base equilibrium in the blood.

It is commonly taught that the thing that really stimulates the respiratory center is not the CO_2 itself, but the slight increase in C_H which, as explained above, inevitably occurs, in spite of the buffer action. This is, however, probably an incorrect view, for R. W. Scott,[6] working in my laboratory, has found that CO_2 itself can excite the center quite independently of the H-ion concentration of the blood. Thus Scott found after injecting sodium carbonate into decerebrate cats until the C_H was very decidedly lowered, that a subsequent increase in the free CO_2 of the blood excited respiration almost to the same degree as would have been the case when the C_H of the blood was the normal, and furthermore, that when this excitement occurred, the blood was still markedly alkaline.

So long then as the center responds immediately to the slight excess of free CO_2 this is got rid of, and the normal ratio between H_2CO_3 and $NaHCO_3$ is reestablished. If the sensitivity of the center should be below par, however, then CO_2 might accumulate in the body and C_H consequently rise. As a matter of fact, even in health, it seems to be established that the excitability of the center may vary, as for example, in relationship to the amount of oxygen in the blood supplying it, and in disease there can be no doubt that such variations in excitability occur. And since we know that the activities of this center are also greatly affected by nerve stimuli, arriving at it along afferent nerves, it is to be expected that it may be keyed up or down in excitability by the state of the nervous system in general. In conditions of nervous excitement and anxiety,

for example, its sensitivity is increased and moderate doses of narcotic drugs, such as morphine, are well known to depress it.

But even were the sensitivity of the center maintained at a constant level, the alveolar-CO_2 would correspond with that of the arterial blood only provided that the exchange of CO_2 across the alveolar epithelium was strictly normal. And when we bear in mind that the proper excretion of the CO_2 in the lungs is dependent upon an accurate adjustment between the heart's action and the rate of CO_2 production in the organism, we see how the mechanism might readily become upset.

Technical difficulties have also to be overcome in the collecting of the alveolar air, for it is now well established that the original method of Haldane and Priestley is approximately accurate only when it is carried out under strictly controlled conditions—so strict that they can not be practiced in the clinic—and even then, as R. G. Pearce, Carter, Krogh, Siebeck and others[7] have shown, we can not be certain of the results. At best, therefore, *the alveolar CO_2 can serve as an accurate index of the acid base equilibrium of the blood only under certain controlled conditions.*

These facts have prompted the most recent observers (Morawitz and Walker[8] and later Van Slyke and Cullen[9]) to return to blood examination for the detection of impending acidosis. The question is what readily measurable property of the blood may we employ? If we return for a moment to the equation $\frac{H_2CO_3}{NaHCO_3} = \frac{1}{20}$ we shall see that when foreign acids combine with the Na of the bicarbonate, this will become replaced by the salts that are formed, such as NaCl, and these will be incapable of acting as buffers. The amount of $NaHCO_3$ present in the blood must, therefore, be a measure of its power to take up such acids without serious disturbance in C_H, which has led Van Slyke to define acidosis as "a condition in which the concentration of bicarbonate in the blood is reduced below the normal level." According to this definition, acidosis is not necessarily an increase in the actual C_H of the blood, or even it is a disturbance in the normal ratio $\frac{H_2CO_3}{NaCO} = \frac{1}{20}$ but is a lowering of the absolute values forming the numerator and denominator of the equation. In brief, it is a lowering of the ability of the blood to take up fixed acid without disturbance in the ratio, a decrease in the reserve alkalinity. The definition is, however, somewhat unfortunate, since it does not include cases in which there is an actual increase in the ratio as a result of the addition of H_2CO_3 to the blood, and such conditions may develop as a result of asphyxia, which, of course, is a common enough cause of acidosis in the broader sense. Moreover, in asphyxial acidosis it may quite well be the case that the $NaHCO_3$ instead of being diminished, is actually increased in the attempt to bring the ratio back to its normal value. When CO_2 is added to blood, for example, it has been shown that the alkali content of the plasma relatively increases, partly because of the migration of K and Na out of the corpuscles into the plasma, and partly because HCl goes in the opposite direction. There can be no doubt, however, that deficiency in bicarbonate is an im-

portant thing to measure as a gauge of the ability of the blood plasma to hold C_H constant when foreign acids are added to it.

In its newer form this test differs considerably from the form in which it was originally employed by Walter (see p. 316), for instead of measuring the CO_2 content of a sample of blood immediately after removal, this is first of all exposed outside the body to an atmosphere containing a known, fixed, percentage of CO_2 until all of the available alkali has become combined with this gas. This procedure removes the most serious objection to the old technic, namely, that the amount of CO_2 in the venous blood,—and that alone is of course available for use in man,—must be very largely dependent upon the rate of oxidation in the tissues, and upon the velocity of movement of blood through the capillaries which drain into the vein. In experimental work on animals, however, the CO_2 actually present in arterial blood remains as the most practical indicator of the buffer action of the blood. Being restricted in man to the use of venous blood, the questions which remain to be answered are: 1. What pressure of CO_2 should be chosen with which to saturate the blood?* 2. Should whole blood or plasma or serum be employed? With regard to the CO_2 pressure, there are two alternatives: we may use either the pressure to which the blood is actually exposed in the organism, the *intra vitam* pressure we may call it, or an arbitrarily fixed pressure. The *intra vitam* pressure of CO_2 can be determined by analysis of the alveolar air, but this, of course, complicates the technic and gives us no more accurate an estimate of the available alkali than when we use the same pressure for all samples.

Concerning the question as to whether whole blood or serum should be used, there can be little doubt that it should be the former. The objection to the use of serum or plasma depends on the fact, as we have seen, that a part of the alkaline reserve resides, not in the fluid menstruum of the blood, but in the corpuscles, and even beyond this, in the tissue cells. It has been known for some time, for example, that when CO_2 is bubbled through whole blood, the alkali content of the plasma decidedly increases, as judged by titration, and when the blood is in contact with the tissue cells it is quite likely that when excess of acid appears in it, there may be a considerable transference, not only of more alkali from the cells into the blood, but also of CO_2 in the opposite direction, (into the cells including the red blood corpuscles) in which it may become combined with alkaline phosphates by such reactions as are illustrated in the equation:

$$Na_2HPO_4 + H_2CO_3 = NaH_2PO_4 + NaHCO_3.$$

It should be remarked that Van Slyke recognizes these possibilities, but nevertheless, he believes that for practical purposes it is allowable to employ venous blood, and to saturate its plasma with CO_2 at a definite partial pressure. The results which he and other workers using his method have employed would certainly appear to justify his claim at least for the detection of cases in which the alkaline reserve is decidedly reduced, but it should not be lost sight of that a strict observance of the principles which we have attempted to explain might

*It may be pointed out, for the sake of those who are not familiar with the work in this field, that the pressure of a gas in a mixture of gases is proportional to its percentage amount; thus 6 per cent CO_2 will give 45.6 mm. Hg pressure at a barometric pressure of 760, for 100 : 760 : : c : x.

make the gauging of the alkaline reserve a still more valuable criterion of disturbances in the acid base equilibrium in the organism.

To sum up, it may be said that determination of the ability of blood to absorb CO_2 is probably the most practical method for measuring the acid neutralizing power; it measures the degree to which the acid buffer can functionate or, as some call it, the alkaline reserve. This high estimate of its value holds good, however, only when the whole blood is taken, but *even then we do not necessarily measure the total reserve of the body*. These reserves are, first, the alkalies of the plasma, second, the alkalies of the corpuscles, third, the proteins of the blood, and the last reserves are probably the alkalies and the proteins of the tissue cells. Now it is clear that there can be no test-tube method by which the magnitude of all of these defensive agencies could be measured; at best we can only measure the first three of them, namely, the reserve power resident in the blood itself. Christiansen, Haldane and Douglas[10] and contemporaneously Morawitz and Walker,[8] have recommended this method, and it is only more recently that Van Slyke, in order to simplify the technic, has advocated the employment of blood plasma (oxalated) alone. Let us consider for a moment, therefore, whether the Van Slyke technic is really much simpler than that employed by Haldane. In the method used by these observers a cubic centimeter, or so, of defibrinated blood is exposed at body temperature for twenty minutes, in an air-tight vessel, to an atmosphere containing a known amount of CO_2. A measured sample is then removed to the gas analysis apparatus of Haldane-Barcroft, and the CO_2 is determined by decomposing the carbonates with strong acid, after getting rid of the oxygen by shaking with ferricyanide solution. The procedure is comparatively simple, and can easily be done with a little practice in the wards.

In Van Slyke's method, the oxalated plasma, separated by rapid centrifuging, is exposed to an atmosphere of expired air in a tonometer, and the plasma then transferred to a gas analysis apparatus, that is certainly no simpler in manipulation than that of Haldane and Barcroft (see Vol. II, p. 55 of this Journal), and which moreover suffers from the disadvantages: first, that the slightest leakages around the stopcock involves a very serious error because of the vacuum which is established in the apparatus at a certain stage of the manipulation, and secondly, that it requires the use of mercury which becomes fouled with the mixture of plasma and acid during the analysis.

Taking into consideration the theoretic objections to the use of plasma or serum in place of blood, and also the doubtful advantage to be gained by using the Van Slyke apparatus, at least by those who are not practiced in the use of gas analysis methods in general, there is no very evident reason why the Van Slyke procedure should be followed in preference to the earlier, really simpler methods of Haldane, etc., and of Morawitz and Walker.

It has been pointed out above that the sensitivity of the respiratory center towards the C_H, or more probably the free CO_2, of the blood is apparently much greater than that of any other center or mechanism in the animal body, and that it is on account of this sensitiveness that the free CO_2 of the blood is immediately got rid of from the body by increased pulmonary ventilation, whenever there is tendency for the C_H to rise above the normal level. As the free CO_2 is got rid of,

the bicarbonate decomposes, because of the presence of other acid groups in the blood, e.g., protein, etc., and the amount that is left indicates the remaining ability of the blood to withstand further addition of foreign acid. Clearly, therefore, the important thing to measure in order that we may be enabled to diagnose the incipient stages of acidosis is the alkaline reserve, and but one question remains to be considered, namely, whether arterial or venous blood should be employed. For various reasons arterial blood is preferable. In the first place the percentage of CO_2 actually present in it is proportional to the alkaline reserve, so that it is unnecessary to expose the blood to an atmosphere containing CO_2 before measuring the CO_2 content, and in the second place, it represents the mixed blood of the body, and not that of only one locality, as is the case with blood removed from a peripheral vein. But in clinical practice venous blood only is available. If this is collected with the precaution that the muscles in the corresponding area have been at rest for some time it appears that there is practically no difference between the alkaline reserve of arterial and venous blood, but if there has been any muscular contraction, the venous blood will have a lower reserve than the arterial, because of the lactic acid thrown into it by the contraction. But even when we take the precaution of avoiding muscular action, it is probable that there is not a strict parallelism between the buffer action of arterial and venous blood as in cases in which the demands on the alkaline reserves are such that those of the tissues are being called on as well as those of the blood itself. The experiment of Van Slyke,[9a] in which he compared actual CO_2-containing powers of arterial and venous blood removed from anesthetized dogs, and found them to be very nearly the same, does not throw any light on this phase of the problem.

The chief criticism against the use of the CO_2 carrying power of blood or blood plasma, is therefore, that it tells little if anything concerning the acid-absorbing powers of the tissues. Is there not, therefore, some test of the acid buffer which can be applied to the intact animal? One such we have already considered, namely, the percentage of CO_2 in alveolar air, and we have seen that it is not entirely satisfactory partly because of the technical difficulties in the collection of the sample of air for analysis, and partly because of possible variations in the sensitivity of the respiratory center. In order to place an estimate on the relative value of these methods comparisons have been made between the CO_2 tension of the alveolar air and the CO_2 absorbing power of the blood. This has been done both in normal and pathologic subjects. In normal subjects the comparisons have been made under conditions, such as the taking of food and during muscular exercise, in which slight alterations in the acid-base equilibrium are known to occur. Van Slyke, Stillman and Cullen[9b] found that the ratio $\frac{\text{plasma } CO_2}{\text{mm. alveolar } CO_2}$ varies from 1.27 to 1.80 in different resting individuals, there being apparently a characteristic ratio for each individual, and that the taking of food invariably raises the alveolar CO_2-combining power. This would seem to indicate that it must be the excitability of the respiratory center rather than the acid base equilibrium that becomes altered so as to cause variations in alveolar CO_2. The same authors, in conjunction with Fitz, working on the above

relationship in patients suffering from diabetes and nephritis, found that in the former disease, under treatment, the alveolar CO_2 tension is often much too low in comparison with the blood bicarbonate. On the other hand the tension is always low in these cases when the bicarbonate content of the blood is low. In nephritis, however, the tension of alveolar CO_2 may be high although the blood CO_2 is low. Peters[12] has also examined these relationships, and has met with many instances where satisfactory parallelism did not exist. One serious criticism of this work is, however, that the method of Fridericia was employed for collecting the alveolar air.

Christiansen, Douglas and Haldane[10] did not find a relation to exist between the CO_2 absorbing power of the blood and the normal resting alveolar CO_2 in different healthy individuals, but after severe muscular exercise, the interesting discovery was made that marked reductions occurred both in the CO_2 absorbing power of the blood, and in the alveolar air, and they suggested "that corresponding differences will probably be discovered under various pathologic or compensatory conditions for acidosis."

In all these comparisons it is with the arterial CO_2 tension that the alveolar CO_2 is believed to run parallel, the air samples being removed from the alveoli under conditions which mean that the gaseous equilibrium must be between alveolar air and arterial blood. The question therefore arises whether more exact parallelism between alveolar CO_2 and blood CO_2 might not be obtained if the venous CO_2 tension were taken instead of the arterial. As shown by Christiansen, Douglas and Haldane, and later by Y. Henderson[11] and R. G. Pearce,[13] the alveolar venous CO_2 tension can be measured by the comparatively simple expedient of causing the patient to inspire an atmosphere containing a percentage of CO_2 above that which corresponds to the free CO_2 of venous blood, and then removing successive samples of the expiration which follows, and analysing each for CO_2. The portions expired at first will contain approximately the same percentage of CO_2 as that in the inspired air, but the percentages will progressively decline in the succeeding portions until at last they become constant at a level which must correspond to the venous CO_2 tension. In the method of Plesch for the collection of alveolar air, in which the person takes several breaths in and out of a rubber bag, the CO_2 percentage of the air in the bag must approximate more closely the CO_2 tension of the venous blood than that of the arterial. It is certainly important that the possibility of a parallelism between alveolar venous CO_2 tension and CO_2 combining power of the whole blood should be thoroughly investigated. On *a priori* grounds the parallelism is likely to be a much closer one than when the comparison is made between alveolar (arterial) CO_2 tension and CO_2 combining power of blood plasma.

By an application of these principles, therefore, it does not appear that there is a simple, thoroughly reliable method by which the buffer action of the body as a whole can be measured. An entirely different plan of attacking the problem must be thought of, namely, to observe the acid excretion by way of the urine.

When we were considering the general nature of the chemical reactions between the salts of the blood and added acid we saw that besides free CO_2 there

would have to be eliminated from the body a considerable amount of acid salts, or of free acids. In this connection the body must be considered as a whole, and when foreign acid is added a corresponding amount must ultimately be eliminated, if the normal acid-base equilibrium is to be reestablished, even although a sudden change in C_H is avoided by the buffer action. Most of this excess of acid, as we have seen, is eliminated by the lungs as CO_2, but the remainder has to be got rid of by other pathways of excretion, particularly the kidneys. The excretion of the acid excess by this pathway occurs in three forms: *first* as acid salts, for example by conversion of Na_2HPO_4 into NaH_2PO_4, *second* as salts of ammonia and *thirdly* as free acid. Concerning the second of these, under normal conditions ammonia is a product of metabolism split off during the break down of amino acids, and then rendered innoxious, by combining with carbonic acid to form ammonium carbonate which is converted into urea, a strictly neutral substance. When excess of acids must be neutralized, however, some of the ammonia instead of combining with CO_2, may be diverted to neutralize the excess, this being particularly the case when ketonic acids appear, as in diabetes. The ammonia excretion itself is, however, no reliable indicator of the amount of free acid in the body, because there are other conditions such as derangement of the hepatic function which may influence it. In the toxic states of pregnancy, for example a large excretion of ammonia may occur without any indication of an acidosis. With regard to the acid which may be excreted in a free state, this occurs, for example, with β-oxybutyric acid, which is so weak in its acid properties, that 45 per cent of it may be excreted in this form.

With such a multiplicity of forms of excretion it is clear that *the only satisfactory method for measuring the acid excretion by the kidney must be one in which all of the above forms of excretion are included.* To measure the amount of free acids and acid salts the theoretically correct method would be to titrate the urine with standard alkali until its C_H, which is normally on the acid side of neutrality, was brought to the same level as that of blood. This can be done by using sulphophenolphthalein which, it will be remembered, changes tint at about the C_H of blood. For practical purposes, however, it has been found more convenient to use phenolphthalein, the neutral point of which is such that when urine just reacts neutral to it, the CO_2 combining power of the blood plasma as tested by Van Slyke's method, is at its maximum by 80 vols. per cent, and the ammonia excretion is zero. By titrating a sample of urine after adding neutral oxalate to it,—in order to precipitate substances which interfere with the sharpness of the end point—with $N/_{10}$ NaOH to the neutral point of phenolphthalein we measure the total of free acids and acid salts, and if we now add to this the amount of ammonia in the same urine, (readily measured by Folin's new permutit method), we obtain the *total urinary acid excretion.* It is said that a definite relationship exists between the CO_2 combining power of the plasma and the total acid excretion, a relationship, however, which can be made clear only when a rather arbitrary equation like that of Ambard is employed. It remains to be seen of what value the determination of this ratio may be in clinical diagnosis.

There remains possible another method for gauging the alkaline reserve, namely, to see *how much alkali can be added to the organism without causing the*

urine to assume an alkaline reaction. When the alkaline reserve of the body is about normal, it is clear that very little alkali will suffice to have this effect. As a matter of fact, it has been found by Sellards[14] and by Palmer and Henderson[15] that only 5 grams a day, can be taken without making the urine alkaline. When the alkaline reserve is seriously depleted, however, large quantities of bicarbonate, even as much as 100 grams a day can be taken without making the urine alkaline. This test has been found of particular value in the diagnosis of acidosis accompanying certain forms of renal disease (chronic interstitial nephritis), which raises the question as to whether the retention may not be due to faulty elimination of the bicarbonate rather than to its retention in order that a deficient alkaline reserve may be corrected. It has not been a very simple matter to entirely disprove this possible explanation, and experiments of a variety of types have had to be devised in connection with the problem. One of them consists in determining the effect of a second dose of bicarbonate administered to an acidosis patient to whom a sufficient amount had previously been given to render the urine just alkaline. It has been found that a few grams now suffice, indicating, apparently, that the alkaline reserve must have been restored to its normal level. Even to this experiment the objection can be raised, however, that the large doses were retained because the threshold of the kidney for the excretion of bicarbonate was a very high one, and that the second, smaller administration just sufficed to overstep this threshold.

Sellards' careful work with this method seems quite clearly to establish its value, however, and for practical purposes *it is no doubt the best test of acidosis at present available in routine clinical work.* It has the important advantage, furthermore, of being simple and of requiring no elaborate apparatus.

Finally it may be advantageous to classify the possible causes which might lead to a want of stability in the C_H of the blood; that is, to threatened acidosis or alkalosis, not of acidosis in the narrow sense implied in Van Slyke's definition, but in the broader sense of any disturbance in the acid-base equilibrium.

In general a tendency to acidosis might be due to an increase in the numerator or decrease in the denominator of the molecular equation $\frac{H_2CO_3}{NaHCO_3} = \frac{1}{20}$, or to a proportionate decrease in both. In the latter case, there would be no actual change in C_H, but the alkaline buffer would be depleted so that the change would very readily set in when foreign acids were added. Furthermore, it should be understood that $NaHCO_3$ only stands as a symbol for all substances that might serve as alkaline reserves, for although this salt is no doubt the most important of these, the alkaline phosphates of the corpuscles, and the protein of the blood and tissues must also be considered. A tendency to alkalosis—which is no doubt extremely rare as a pathologic condition—would be due to changes of a reverse character. A theoretic classification of the conditions which might cause these changes is given:

Increase of C_H.

Addition or accumulation of acid	Accumulation of CO_2 (asphyxial conditions).
	Incomplete oxidation of carbohydrate (lactic and in muscular exercise).
	Defective oxidation of fat (ketosis).
	Renal insufficiency (nephritis).
	Decomposition of protein (as in acidosis of fever).
	Intestinal fermentation.
	Administration of acid (experimental).
Decrease of base	Diarrhea and hemorrhage, respectively (may explain acidosis in cholera and in certain forms of shock).

Decrease in C_H.

Addition or accumulation of base	Ammonia (faulty metabolism of urea).
	Intestinal putrefaction (infantile conditions).
	Administration of alkalies (experimental).
Removal of acids	Excretion of CO_2 (excessive pulmonary ventilation, as in faulty ether administration).
	Excretion of acid urine.

BIBLIOGRAPHY

[1]Naunyn, B.: Der Diabetes Mellitus, Vienna, 1906.
[2]Haldane, J. B., and Priestly. J. P.: Jour. Physiol., 1905, xxxii, 227.
[3]Beddard, Pembrey and Spriggs: Jour. Physiol., 1904, xliv, 31; ibid., 1908, xxxix, 37; also Brit. Med. Jour., 1908, ii, 580.
[4]Levy, R. L., Marriott, W. McKin., and Rowntree, L. G.: Arch. Int. Med., 1915, xvi, 389. Clark and Lubs: Jour. Bact., 1917, ii, 1 and 109.
[5]Henderson, L. J.: Am. Jour. Physiol., 1905-06, xv, 257; ibid., 1908, xxi, 169 and 427; Jour. Biol. Chem., 1909, ix, 403.
[6]Scott, R. W.: Am. Jour. Physiol., 1918, xlvii, 43.
[7]Pearce, R. G.: Am. Jour. Physiol. 1907, xliii, 73; ibid., xliv, 369.
Hoover, D. R.: ibid., 391.
Krogh, A., and Linhard, J.: Jour. Physiol., 1914, xlvii, 431.
Haldane, J.: Am. Jour. Physiol., 1915, xxxviii, 20.
Carter, E. P.: Jour. Exper. Med., 1914, xx, 81.
[8]Morawitz, P., and Walker, J. C.: Biochem. Ztschr., 1914, lx, 395.
[9]Van Slyke and Cullen: Jour. Biol. Chem., 1917, xxx, 289.
[9a]Van Slyke and Cullen: Loc. cit., p. 363.
[9b]Van Slyke, Stillman and Cullen: Jour. Biol. Chem., 1917, xxx, 401.
[10]Christiansen, J., Douglas, C. C., and Haldane, J. B.: Jour. Physiol., 1914, xlviii, 246.
[11]Henderson, Y.: Jour. Biol. Chem., 1917, xxxii, 325.
[12]Peters, J. P.: Am. Jour. Physiol., 1917, xliii, 113.
[13]Pearce, R. G.: Proc. Am. Phy. Soc., Am. Jour. Physiol., 1918, xlv, 550.
[14]Sellards, A. W.: Principles of Acidosis, etc., Harvard University Press, 1917.
[15]Henderson Y., and Palmer: Jour. Biol. Chem., 1912, xiii, 393; ibid., xiv, 81; ibid., xvii, 305; ibid., 1915, xxi, 37.

THE EPIDEMIC OF INFLUENZA AT CAMP DEVENS, MASS.*

By Paul G. Woolley, M.D. (Cincinnati, Ohio)
Major, M.C., Camp Sanitary Inspector and Epidemiologist, Camp Devens, Mass.

THE epidemic of influenza and pneumonia which attacked Camp Devens was a part of the pandemic which swept across the United States in the late summer and early fall of 1918. Camp Devens was the first of the cantonments to be affected, and since no warning had been given, and no data regarding treatment or prophylaxis had been promulgated, the camp authorities were unembarrassed and unassisted by precedents in the management of the epidemic.

The disease appeared in the camp, as far as can be seen, on the eighth of September. It reached its acme on the sixteenth, seventeeth and eighteenth of the month and then rapidly declined, almost completely vanishing about the middle of November. The first cases were observed in members of Company B, 42nd Infantry. On September 7 a case of epidemic meningitis had been sent to the Base Hospital from this company. On the following day a dozen other members of the same company had been sent to the hospital for observation for meningitis, but these twelve proved to be merely what was called at the time, "nasopharyngitis, acute, catarrhal." Subsequent developments showed that the nasopharyngitis of this period was in reality mild "Spanish influenza." A definite diagnosis of influenza was made on September 12. On September 9, five more suspicious cases were sent to the hospital from the same company, and so on, until by September 16, thirty-six members of the one company had received hospital attention. Meanwhile, however, similar cases were being observed and sent to the hospital from other regiments and organizations, a state of affairs that brought about a sudden change in the general sick rate as shown in Table I of hospital admissions. The figures in this table will indicate the sudden and enormous strain which was thrown upon the hospital.

Table I

Hospital Admissions

September 1	39	October 8	78
2	31	9	79
3	51	10	100
4	80	11	68
5	78	12	81
6	95	13	51
7	95	14	58
8	93	15	80
9	93	16	69
10	142	17	75
11	186	18	78
12	227	19	59
13	350	20	51
14	502	21	36

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TABLE I—(Cont'd)

HOSPITAL ADMISSIONS

September	15	705	October	22	87
	16	1189		23	66
	17	1056		24	74
	18	1176		25	70
	19	624		26	59
	20	778		27	48
	21	684		28	45
	22	443		29	86
	23	578		30	91
	24	505		31	83
	25	386	November	1	65
	26	239		2	50
	27	173		3	47
	28	117		4	31
	29	117		5	73
	30	74		6	62
October	1	126		7	50
	2	93		8	54
	3	94		9	50
	4	76		10	40
	5	76		11	29
	6	78		12	49
	7	50			

These early cases of "nasopharyngitis" were looked upon at first as examples of the mild epidemic disease which had attacked many of the cantonments during the spring of 1918. At that time very many soldiers were affected by what seemed to be severe but transient "colds" without coryza. With this disease there were no fatalities. It may be justifiable to surmise that the cause of the mild but extensive spring epidemic was an attenuated or avirulent form of the organism which has been responsible for the recent epidemic, and that it became more virulent in the course of repeated passages from host to host. However that may be, it was not immediately realized that we were dealing with such an exceedingly serious disease until the complicating pneumonias began to appear in steadily increasing numbers, and this was not until after the epidemic had gathered headway of considerable proportions. Table II shows the number of new cases of pneumonia reported by the Base Hospital:

In the first week of September the pneumonias were evidently on the increase but for that there seemed to be perfectly good meteorologic and racial reasons. Of the cases appearing during the first fourteen days of September, 44 were in negroes,—a little over 50 per cent. Of the 25 cases occurring during the first seven days of the month, 16 were in negroes. And then it became increasingly evident that the mass of the pneumonias were very definitely related to the influenza. The evidence for this was (1) the ever-increasing number of pneumonias in patients who had been admitted for influenza; (2) the number of men who, upon admission, had both "flu" and pneumonia; (3) the number of men who were discharged from the hospital convalescent from "flu" who were readmitted for pneumonia; (4) the type of pulmonary lesions, as found at autopsy; (5) the bacteriologic findings.

The disease was no respecter of persons except that it was more severe

TABLE II

PNEUMONIA CASES

September	1	4	
	2	1	
	3	4	
	4	2	
	5	2	
	6	0	
	7	12	
	8	7	
	9	7	
	10	6	
	11	8	
	12	7	
	13	9	
	14	18	
	15	17	
	16	17	
	17	26	
	18	43	
	19	38	
	20	87	
	21	118	
	22	176	
	23	215	
	24	342	
	25	309	
	26	221	
	27	79	
	28	106	
	29	47	
	30	111	
October	1	74	
	2	31	
	3	28	
	4	16	
	5	13	
	6	10	
	7	4	
	8	17	
	9	4	
	10	7	
	11	7	
	12	4	
	13	9	
	14	1	
	15	17	
	16	5	
	17	3	
	18	8	
	19	3	
	20	5	
	21	3	
	22	3	
	23	5	
	24	3	
	25	5	
	26	5	
	27	6	
	28	6	
	29	3	
	30	5	
	31	7	
November	1	13	
	2	5	
	3	4	
	4	1	
	5	6	
	6	3	
	7	2	
	8	4	
	9	2	
	10	1	
	11	2	
	12	2	

in those who were hard workers. Those who tried to "buck the game" and "stay with it" showed the highest mortality rates. So, the noncommissioned officers and the nurses suffered more severely than the commissioned officers and privates.

TABLE III

COMPARATIVE MORTALITIES

Commissioned Officers	
Average strength	1194
Total pneumonia cases	30
Annual morbidity rate per 1000	261
Deaths	8
Annual mortality rate per 1000	69
Case mortality	26.8%
Noncommissioned Officers	
Average strength	3493
Total pneumonia cases	70
Annual morbidity rate per 1000	208
Deaths	28
Annual mortality rate per 1000	83
Case mortality	40%

Nurses	
Average strength	225
Total pneumonia cases	9
Annual morbidity rate per 1000	416
Deaths	3
Annual mortality rate per 1000	77
Case mortality	33.3%
White Enlisted Men	
Average strength	41,321
Total pneumonia cases	2,261
Annual morbidity rate per 1000	568
Deaths	388
Annual mortality rate per 1000	145
Case mortality	26%
Black Enlisted Men	
Average strength	3074
Total pneumonia cases	334
Annual morbidity rate per 1000	1130
Deaths	75
Annual mortality rate per 1000	253
Case mortality	22.5%

NOTE: The above figures are for the period of five weeks from August 28 to October 1, 1918. They cover the most active portion of the epidemic but are obviously incomplete. They are given only for comparison.

Although the first cases of influenza appeared suddenly in a single company of the 42nd Infantry, it was but a few days until practically every organization, large and small, in the camp was affected, as the following tables will show. The figures used are the rates per 1000, for the days indicated, of total sick,—in other words it is the noneffective rate that is given and not the isolated influenza rate. The noneffective rate is given, in spite of the slight inaccuracy in applying it to influenza, because it is felt that the number of "all other diseases" helps to balance the number of unreported influenzas, i. e., mild cases which despite every effort were overlooked and so failed to be shown on the returns. However that may be, the variation from the exact truth would be so small that the end results would be prejudiced not at all.

TABLE IV

ORGANIZATIONAL NONEFFECTIVE RATES

	Infantry				Mch. Gun Bns.			Engi-	Supp.	Trns.
	36	42	73	74	34	35	36	neers	Trn.	M. P.
Sept. 1	15	21	14	13	—	24	23	—	16	—
2	15	21	14	13	—	23	21	—	11	—
3	14	23	14	14	2	23	23	2	11	—
4	14	25	15	14	2	27	24	2	11	—
5	14	25	18	14	5	21	26	2	5	36
6	14	30	18	15	5	21	23	5	5	35
7	14	30	19	16	4	15	23	7	5	31
8	14	28	19	17	4	16	21	11	5	31
9	15	30	21	18	4	21	23	12	5	33
10	16	32	21	18	4	30	21	13	2	30
11	15	34	22	20	2	38	22	15	6	36
12	15	37	27	24	6	49	35	17	26	41
13	15	37	38	34	10	68	—	23	75	52

TABLE IV—(Cont'd)

ORGANIZATIONAL NONEFFECTIVE RATES

		Infantry				Mch. Gun Bns.			Engi-	Supp.	Trns.
		36	42	73	74	34	35	36	neers	Trn.	M. P.
Sept.	14	14	37	45	50	10	93	—	32	85	58
	15	15	39	67	62	10	123	35	50	101	118
	16	21	64	105	77	25	227	86	76	120	160
	17	35	106	157	106	85	285	109	173	110	210
	18	44	119	196	150	116	230	106	206	168	250
	19	52	141	244	164	126	236	121	182	189	225
	20	62	153	252	204	146	320	137	182	133	232
	21	70	163	241	206	150	190	140	174	130	236
	22	63	151	251	191	150	151	161	200	115	238
	23	75	160	259	226	176	204	170	241	133	241
	24	77	172	256	238	184	205	174	273	124	245
	25	78	156	243	243	176	190	158	278	111	239
	26	78	156	217	244	179	190	167	287	112	239
	27	76	154	196	262	184	158	165	286	97	243
	28	80	169	186	268	160	163	171	286	98	234
	29	76	146	177	202	146	147	156	275	95	233
	30	75	139	180	180	120	150	157	270	69	214
Oct.	1	72	134	171	168	125	136	144	271	71	209
	2	74	102	123	80	114	134	156	281	72	205
	3	74	96	120	78	108	87	156	290	69	202
	4	81	89	118	72	94	84	104	178	—	194
	5	78	85	120	70	92	82	123	157	75	193
	6	70	65	120	70	89	83	107	157	61	190
	7	63	71	110	68	79	98	100	122	61	202
	8	42	72	113	65	73	82	94	120	57	186
	9	42	72	104	63	73	86	88	—	57	157
	10	39	69	105	62	67	—	83	—	57	172
	11	38	67	105	61	59	79	75	105	57	170
	12	36	60	104	60	59	74	69	92	59	169

(N. B. All of the above organizations are parts of the 12th Division.)

TABLE V

ORGANIZATIONAL NONEFFECTIVE RATES

		Camp	Depot Brig.	13th Bn.	Dev. Bn.	Q.M.C.	A.R.D.	12th Division
Sept.	1	31	62	161	66	12	13	15
	2	32	60	153	67	14	15	16
	3	32	60	158	68	14	12	16
	4	32	58	160	66	13	10	17
	5	31	54	160	61	13	10	17
	6	31	53	160	61	12	10	19
	7	32	55	162	60	12	8	20
	8	32	56	166	62	12	8	19
	9	34	57	170	68	12	8	20
	10	33	61	175	68	11	8	21
	11	35	66	177	78	12	10	22
	12	38	70	176	88	12	12	24
	13	40	60	131	93	20	12	28
	14	48	72	139	110	25	12	34
	15	63	94	159	112	34	13	43
	16	86	113	181	115	34	13	65
	17	105	141	212	150	37	17	96
	18	125	161	250	158	43	26	125

TABLE V—(Cont'd)

ORGANIZATIONAL NONEFFECTIVE RATES

		Camp	Depot Brig.	13th Bn.	Dev. Bn.	Q.M.C.	A.R.D.	12th Division
Sept.	19	156	201	273	165	51	36	152
	20	179	231	282	166	55	58	172
	21	190	255	284	179	59	67	181
	22	196	260	290	177	56	55	166
	23	185	265	294	180	59	71	181
	24	189	268	300	190	60	76	193
	25	187	266	274	191	51	76	194
	26	185	224	240		49	76	190
	27	185	224	230		45	76	188
	28	185	202	167		40	74	187
	29	150	174	159		36	74	168
	30	127	136	161		35	72	157
Oct.	1	120	132	159		29	69	150
	2	116	127	158		30	56	140
	3	106	121	158		27	54	117
	4	103	117	158		29	50	113
	5	100	109	135		28	54	100
	6	92	106	117		29	52	95
	7	91	104	114		30	68	93
	8	87	102	114		35	68	85
	9	85	96	115		32	64	83
	10	81	91	115		27	59	79
	11	79	87	110		27	58	77
	12	79	90	106		29	49	71

(N. B. It is to be remembered that the camp includes all the organizations. The 13th Battalion, composed entirely of negro troops, and the Development Battalions are parts of the Depot Brigade. The Quartermaster's Corps and the Auxiliary Remount Depot are independent organizations. The Division includes all the other organizations tabulated.)

It will be seen from the foregoing figures that for a while the epidemic was slowly extending and that it finally acquired an almost explosive character, so that—

On September 17, 28.2% of the 35th M. G. Bn. was sick;
On September 19, 18.9% of the 212th Supply Train was sick;
On September 23, 26.0% of the 73rd Infantry was sick;
On September 24, 29.6% of the 13th Battalion was sick;
17.3% of the 42nd Infantry was sick;
18.0% of the 34th M. G. Bn. was sick;
17.4% of the 36th M. G. Bn. was sick;
13.3% of the A. R. D. was sick;
6.0% of the Q. M. C. was sick;
19.1% of the Dev. Bns. was sick;
24.6% of the Trains & M. P. was sick;
On September 25, 28.2% of the Field Signal Bn. was sick;
27.8% of the 212th Engineers was sick;
On September 26, 24.2% of the 74th Infantry was sick;
On September 28, 8.0% of the 36th Infantry was sick;

or, put in another way—

On September 22, 19.6% of the total camp personnel was sick;
On September 24, 19.4% of the 12th Division was sick;
26.8% of the strength of the Depot Brigade was on sick report.

The preceding figures give some idea of the rapidity of spread of the disease and of its extent in the camp. In all more than 30 per cent of the population was affected. Roughly speaking the rise of the curve occupied the interval between September 8 and September 17; the crest extended over the five days from September 17 to September 21. The fall was at first abrupt for seven to eight days and then more gradual extending over several weeks.

On	September	18,	6674	cases	had	been	reported.
"	"	19,	there	were	1184	new	cases.
"	"	20,	"	"	1543	"	"
"	"	21,	"	"	1179	"	"
"	"	22,	"	"	868	"	"
"	"	23,	"	"	616	"	"
"	"	24,	"	"	458	"	"
"	"	25,	"	"	271	"	"
"	"	26,	"	"	240	"	"
"	"	27,	"	"	153	"	"
"	"	28,	"	"	221	"	"
"	"	29,	"	"	107	"	"
"	"	30,	"	"	38	"	"

From September 30 on there were a few less cases each day or so, with occasional rises until the latter part of October and the first of November when they practically disappeared.

The epidemic persisted for a shorter period in the camp than it did in the surrounding cities, including Boston, because the population of the camp was more concentrated, and also because less was undertaken in the way of quarantine than in those centers. It was apparent that the disease was everywhere in the camp almost from the start and therefore the energies of the surgeons were expended upon treatment rather than upon other measures. Comparative studies indicate that the procedures were justified.

So far as is known there were no fatalities from uncomplicated influenza. In every fatal case but two a diagnosis of pneumonia was made, and in these two cases pure cultures of pneumococcus were obtained from the blood after death, so that it appears that they were cases of pneumococcus septicemia. In all, 2817 cases of pneumonia were reported in connection with the epidemic covering the period ending October 29, a figure which represents about 19 per cent of the total number of influenza cases reported during the period. Of these 787 died—a case mortality of 27.9 per cent and about 5.4 per cent of the influenza cases. The pneumonias were of two types—lobar and lobular (or broncho), the latter predominating in the white men, the former in the negroes. The characteristic cases in white men seems to have been a pseudolobar pneumonia, which accounts for the frequent clinical diagnosis of lobar pneumonia, while in the negroes the typical lesion was perfectly frank lobar consolidation. The latter seems to cause a lower mortality in the negroes than the former does in the whites, and so the difference in mortality in the two races is most readily explained.

Table VI shows the number of cases of pneumonia in the Base Hospital from day to day, and will serve to indicate the enormous burden thrust upon the personnel of that institution.

TABLE VI

PNEUMONIA CASES IN HOSPITAL AND THE PNEUMONIA RATE PER 1000 FOR EACH DAY

	Cases	Rate per 1000
September 1	127	2.9
2	128	3.0
3	130	3.0
4	128	2.9
5	129	2.8
6	142	3.1
7	152	3.3
8	159	3.5
9	164	3.6
10	168	3.6
11	174	3.8
12	176	3.8
13	185	4.0
14	146*	3.2
15	161	3.6
16	169	3.8
17	191	4.2
18	228	5.1
19	260	5.7
20	348	7.6
21	442	9.7
22	581	12.8
23	727	16.0
24	992	21.8
25	1215	26.7
26	1355	29.8
27	1902**	41.7
28	1933	42.5
29	1928	42.5
30	1993	44.2
October 1	2033	44.7

After October 1, the number of cases of pneumonia in hospital gradually decreased.

Pneumonia was already present in the camp when the epidemic of influenza appeared. It was widely scattered and was concentrated at but one point in the camp, i. e., in the 13th Battalion of the Depot Brigade, an organization composed entirely of negroes, most of them from Florida and the South. This battalion had just passed through an epidemic of pneumonia and was just about out of the woods when influenza attacked it. The result was striking. It seems certain that many of the blacks were harboring the pneumococci, which were only waiting a favorable opportunity to invade their hosts. Influenza furnished the required opportunity. Among the white men the conditions were somewhat different. In this group of the camp population there had been some cases of pneumonia but not many, and they were scattered, and the death rate was exceedingly low. Still, the pneumococci were evidently widespread in the camp and always a possible source of danger. It is interesting that under these circumstances the two races should suffer as they did, the white men

*At this time a considerable number of late convalescent pneumonias were discharged to make room for acute cases.

**This figure is due to taking up a number of previously unreported cases, unreported because of the clerical breakdown. They were not unrecognized or untreated cases.

from a lobular (influenzal?) type, and the negroes from a typical lobar type.

Pneumonia was a very early complication in a great many cases, though because of its early anatomic distribution it was frequently difficult to diagnose it by the usual methods of auscultation and percussion. Because of the fact that it usually develops centrally or near the hilus and progresses outward toward the pleura, it is apt to be overlooked. Nevertheless in very many cases sent to the hospital for influenza, pneumonic consolidation was discovered at the receiving station. For instance, in the records of seven days there were 139 cases diagnosed pneumonia on admission. At Camp Devens it was the rule to take no chances with influenza, and to send cases to the hospital as soon as possible. These cases justified the rule, if justification were needed, for it became very apparent that every case of influenza should be treated as a possible pneumonia until careful observation proved the contrary. The great variation in the time which might elapse in the development of these consolidations is shown in the following figures which were obtained early in the epidemic:

Diagnosis of pneumonia made	
On day of admission	1
On day after admission	41
Second day after admission	101
Third " " "	77
Fourth " " "	56
Fifth " " "	101
Sixth " " "	89
Seventh " " "	85
Eighth " " "	51
Ninth " " "	18
Tenth " " "	9
Eleventh " " "	1
Twelfth " " "	2

There seems to be very good and sufficient reasons for believing the influenza was introduced into Camp Devens from Boston. It is, however, impossible to decide whether the infection was carried into the camp by members of the civil community who had come to visit friends in the camp, or by soldiers who had been out of camp on leave. On Saturdays and Sundays there are enormous numbers of visitors to the camp, and also large numbers of passes are granted to soldiers for those days. At any rate the epidemic can not be attributed to conditions within the camp. *Overwork and fatigue* have had no appreciable effect upon the epidemic nor in leading up to it. During the epidemic two hikes were indulged in by the two infantry brigades of the command. On September 20 the 23rd Brigade marched to Cranberry Pond, about five miles from the camp, spent the night in the rain under shelter tents, and returned the following day. On September 28 the 24th Brigade took the same trip. In neither case were any bad results observed by the ever-watchful Division Surgeon. Previous to the hikes the commands were carefully overhauled and every man concerning whom there was the slightest doubt was left behind in quarters. It is this weeding-out that accounts for the rise of the noneffective rate on appropriate days. The *weather conditions* seemed to many to be accountable for a great deal of sickness, for the spread of influenza, and for the frequency of pulmonary complications. An analysis of the data does

not confirm this except in those cases where the men were allowed to take advantage of the execrable weather to remain indoors. The organizations which spent most of the time in the open, and which were therefore most exposed to the weather, suffered least during the epidemic (note the Remount Depot). Fresh air is one factor in this, but separation of individuals is accessory. *Housing*, if one includes in the term overcrowding, has surely been an important factor in spreading the epidemic. Whether it has had any appreciable effect upon the incidence of complications is a question. The epidemic has certainly gone faster and was over sooner because of the crowding; the hospital was filled sooner than it should have been as a result of the rapidity of spread of the disease, and overcrowding of the hospital occurred when with a less rapid spread it would not have occurred; but whether the number of fatalities or the number of pneumonias was greater than they should have been with less crowded conditions may be doubted. Camp Devens was constructed for a maximum population of 35,000 men. At the time of the epidemic there were 45,000 men in it. But the conditions are not told merely by the numbers. Five thousand of the overpopulation were in tents, and this reduced the overcrowding to 5,000. If the weather conditions had not been so miserable just prior to the outbreak of influenza, most of the additional 5,000 would have been in

TABLE VII

EFFECT OF LENGTH OF SERVICE

A. Length of service in men who died of influenza-pneumonia:

Less than 1 month	38
1 month	130
2 months	241
3 months	72
4 months	46
5 months	21
6 months	12
7 months	5
8 months	3
9 months	0
10 months	3
11 months	2
12 months	14
More than 12 months	4
Not given	30
Total	621

B. Data from the Infantry Organizations:

36th Infantry	Strength 3781		
Less than 5 months'	service	975	Influenza 264
More " " "	"	2806	" 302
42nd Infantry	Strength 3757		
Less than 5 months'	service	2182	" 611
More " " "	"	1575	" 124
73rd Infantry	Strength 4241		
Less than 5 months'	service	3593	" 1257
More " " "	"	648	" 210
74th Infantry	Strength 3723		
Less than 5 months'	service	2809	" 1443
More " " "	"	914	" 397

tents. Before the arrangements could be made the epidemic opened. The large number of *recruits* in the camp certainly was a factor in increasing the disease incidence, as shown in Table VII.

Associated with the problem of the recruit is that of *individual susceptibility*. This element is to be evaluated with the greatest circumspection. There are no definite facts to indicate that there are or are not individuals who are not susceptible to the infection. Not until the laboratory has some more definite information concerning the cause will we be able to discuss this question with any degree of satisfaction. For the present it seems that multiplied opportunities for infection play a more prominent role than susceptibility. The *general sanitary conditions* of the camp were excellent before and during the epidemic. The buildings were kept sufficiently warm and at the same time decent ventilation was enforced. It was the rule to require that at least 50 per cent of the upper sashes in each squad room should be kept open during the night. Beds and bedding were taken out of doors and aired on every available day. Tents were kept open as a rule, and were furled on every sunny day. Clothing was ample and there was a sufficient amount of bedding for each man. There was but little dust in the camp, partly because of the general situation of the camp, but largely because of the amount of rain. The barracks were wet-swept and mopped with mixtures of soap suds and oil. There were no mosquitoes and but few flies. The quality and quantity of food was all that could be desired. Promptly after the onset of the epidemic all bunks were separated by shelter tent halves. The men slept with heads and feet alternating.

The problem of the effects of previous life in *cities or in rural districts* was studied superficially as shown in Table VIII.

Very early in the epidemic bacteriologic studies were started. At first these were centered upon the blood and were unproductive—all cultures made from the blood during life remained sterile. Attention was then focused upon the sputum, which, while it had been studied from the start with reference to pneumococcic types, had not been systematically examined for other germs. It was immediately plain that beside the pneumococci and hemolytic streptococci, the sputum contained a small delicate bacillus which was apparently identical with that of Pfeiffer. The coexistence of these various organisms made it a difficult task to isolate the last. From the consolidated lungs three organisms were isolated at autopsies—the pneumococcus, the bacillus of Pfeiffer (?), and a larger bacillus as yet unidentified. From the blood of the heart pneumococcus alone was isolated. Early in the epidemic the routine work claimed every available worker. Later, however, additional and expert assistance was furnished. It is interesting to consider that the streptococci though present in so many mouths seemed to play no part in the pathologic changes found at autopsy. A different state of affairs may develop at other camps.

Special reports on the bacteriology and pathology of the epidemic will undoubtedly soon issue from the laboratory of the Base Hospital. The notes made here are very incomplete. In the postmortem reports filed in the office of the Camp Surgeon the anatomic diagnosis "lobar pneumonia" appears in about two-thirds of the cases. In the remaining third lobular, broncho, or con-

fluent pneumonia are given as the cause of death. It is believed that the essential lesion is a focal one—lobular—which in the course of events may, and does in a considerable number of cases, become more or less lobar in its distribution. The appearances suggest that the pulmonary disease begins as a very severe, and often hemorrhagic, inflammatory edema primarily lobular in distribution, and definitely related to the bronchi. The lungs are intensely congested and even quite generally hemorrhagic but with focal areas of consolidation in the

TABLE VIII

DATA ON URBAN AND RURAL PNEUMONIA DEATHS IN CAMP DEVENS

A. The following data bear upon the distribution of influenza-pneumonia in urban and rural populations. The population figures are not exact and were derived from several sources. They are, however, believed to be sufficiently accurate to serve the purpose for which they were used. All the deaths occurred at Camp Devens.

STATE	POPULATION	DEATHS	RATE PER 100,000
New Hampshire	442,500	43	9.7
Urban	188,900	15	7.9
Rural	253,600	28	11.1
Maine	792,400	115	14.5
Urban	183,900	18	9.7
Rural	608,500	97	15.9
Vermont	363,000	47	12.9
Urban	48,600	5	10.3
Rural	314,400	42	13.3
Massachusetts	3,729,000	215	5.7
Urban	2,585,500	141	5.4
Rural	1,133,500	74	6.5
Connecticut	1,244,500	66	5.3
Urban	597,000	30	5.0
Rural	647,500	36	5.5
Me., N. H., Vt., Mass., Conn.	6,571,400	486	7.3
Urban	3,603,900	209	5.8
Rural	2,967,500	277	9.4

B. The following data bear upon the distribution of influenza-pneumonia in urban and rural populations in Massachusetts. There are not sufficient data available to make a similar comparison in the other New England states.

CITIES	TOTAL POPULATION	DEATHS	RATE PER 100,000
Over 100,000	1,700,000	75	4.4
50,000-100,000	220,000	10	4.5
40,000- 50,000	236,000	12	5.1
30,000- 40,000	143,480	12	8.3
20,000- 30,000	94,500	9	9.5
10,000- 20,000	191,480	23	12.0
Total	2,585,460	141	5.4

TOWNS	POPULATION	DEATHS	RATE PER 100,000
5,000-10,000	128,000	23	17.9
2,000- 5,000	11,500	5	42.6
Total	139,500	28	20.0
Other Towns and Villages	1,004,040	46	4.5

C. It is only in the group of deaths for "other towns and villages" that any discrepancy exists in the series, and this discrepancy can not be explained unless it is possible that the places belong in one of the two former groups. They may be suburbs, for instance, of larger towns and cities.

region of the hilus. They have many of the characteristics of the lungs of animals suffering from hemorrhagic septicemia. From the hila the inflammatory changes appear to extend peripherally following the bronchi. Such true consolidation as occurs is patchy and the areas do not have the gray, dryish, granular appearance of the usual lobar pneumonia. Upon the pleuræ there may be scanty collections of fibrin, and in the pleural cavities there are apt to be accumulations of clear serous fluid. Pericarditis does not seem to be common. The main bronchi, and often the larynx and pharynx are quite congested and even hemorrhagic, a condition which may account for the presence of bright blood in the sputum in many cases. The cervical and peribronchial lymph glands are congested and, at least in some instances, studded with foci of necrosis so that they resemble lesions found in plague.

While it is true that the Medical Department bore the brunt of the fight against the epidemic, it is also true that without the help of the line, officers and men, the battle would have been lost. The line cooperated to the fullest possible extent and helped in every possible way. Nevertheless the strain upon the Medical Department was almost unbearable. At first there were not enough doctors and nurses. Later this lack was corrected.

During the epidemic the regimental infirmaries were kept running day and night, and were subject to inspection at any time in the twenty-four hours. Scarcely a night passed that some one from the Camp Surgeon's office did not drop in at the various infirmaries to see that the work was going on, and to go out with the Surgeon to the barracks to see if any one in need of attention was being overlooked and to see that the squad rooms were in proper order and were well ventilated. On these trips any man who even looked as though he might be sick was examined and if he showed any definite signs he was sent to the hospital or placed in an isolation room for observation. In order to provide for such a continuous medical service for the more than 40,000 men the members of special boards were detailed to the infirmaries or to the Base Hospital. It came about in this way that every medical man in the camp was on constant active duty at the height of the epidemic. The Camp Surgeon was indefatigable in his efforts to see that everything was done that could be done, and deserves the most unstinted praise.

Methods of isolating the bunks in barracks in attempting to control the epidemic have already been mentioned, as have other sanitary methods. Preventive measures other than separating beds, keeping the men out of doors as much as possible, and separating them at mess, do not seem to have been valuable—at least they have shown no decided effects. Just what the study of the whole situation will show the value of masks to have been, remains to be seen. At Camp Devens they were not used. We felt that masking might well be useful provided the masks were properly made and if they were worn with military precision. During such a period of stress as that which prevailed during the epidemic this could not be accomplished. In the Base Hospital previous to this epidemic the surgeons and nurses and attendants have worn no masks and have escaped pneumonia and other diseases very consistently. During the epidemic they did wear them and they have suffered severely from the disease. Visitors at the hospital were required to wear masks. At no time

were the entertainment buildings closed to men, but all gatherings were interdicted and no entertainments were given. Visiting within the camp was permitted only to friends of men on the dangerously sick list.

In conclusion only this can be said, that the epidemic hit Camp Devens at a time when it was unexpected. The attack was unheralded from any source and there were no precedents to guide in its management. From the start more emphasis was placed upon early recognition and hospitalization, and every case was looked upon and treated as a potential pneumonia. Little emphasis was placed upon quarantine and preventive measures except those which kept men out of doors as much as possible and those which kept men apart in barracks and mess halls.

Table IX contains a statistical summary of the epidemic by weeks.

TABLE IX

	SEPT. 4-10	SEPT. 11-17	SEPT. 18-24	SEPT. 25-OCT. 1	OCT. 2-8	OCT. 9-15	OCT. 16-22	OCT. 23-29	SEPT. 4 OCT. 29
Average strength of command	45096	44565	45380	45347	45153	44450	43383	41145	44315
Average white strength	42005	41478	42307	42037	41836	41113	40013	38625	41192
Average black strength	3091	3087	3073	3310	3317	3317	3270	2520	3123
Total influenza cases			*12924	1076	289	135	92	67	14583
Total pneumonia cases	49	102	1020	1415	119	49	30	33	2817
Annual rate per 1000 (pneumonia)	76	157.5	1548	2182	136.9	77.2	34.9	42.3	413
Total pneumonia deaths	3	8	212	437	94	24	5	4	**787
Annual mortality rate per 1000—pneumonia	3.4	9.3	242.2	500	108.2	28.1	6.1	5.9	114
Total black pneumonias	25	30	126	62	25	6	6	18	298
Annual rate per 1000—black pneumonia	421	504	2127	978	393	94.4	95.4	372	619
Black pneumonia deaths	3	0	29	37	12	4	0	2	***87
Annual rate per 1000 black pneumonia mortality	50.4	0	490	581	188	62.6	0	41.2	183
Total white pneumonias	24	72	894	1353	94	43	24	15	2519
Annual rate per 1000	29.7	90.2	1075	1673	116	54	31	20	53.5
Total white pneumonia deaths	0	8	183	400	82	20	5	2	700
Annual rate per 1000	0	10.2	224	494	101	25	6.4	2.7	14.9

*Includes cases reported since Sept. 4.
** = 27.9% case mortality.
*** = 29.5% case mortality.

APPENDIX

Since the preparation of the above notes, a superficial study has been made, which was perforce largely retrospective, of the part played in transmission of disease by methods of washing dishes in the various messes. It may be said, that generally speaking, the common method of washing mess kits is for each man to wash his own kit, and this he does by passing in line before a series of large cans filled with hot water, into which he dips his utensils. The first two of the series of cans are filled with hot, soapy water; the last, with clear, hot water. An alternative method consists in pooling the mess kits and having them washed in the kitchen by the kitchen police. The latter method pre-supposes a better supply of hot water, so that after the final rinsing the kits are drained and dried, and dish towels are done away with. Where this alternative method has been used, the influenza rate has been said to be lower than when the common method is in use (see Lynch and Cumming: *The Military Surgeon*, Dec., 1918, xliii, 597). Special investigation of this aspect of the question indicates that at the Remount Depot, the Quartermaster Corps messes, and in the messes of the 36th Infantry, greater care was exercised in the washing of mess kits, and that at the Remount Depot and Quartermaster Corps, the mess kits were, almost without exception, pooled.

It seems from the indications to date that the matter of hand-to-food, and hand-to-dish transmission is one that may well be considered by health authorities (note its importance at public eating places) and by individuals in their houses.

THE NATURE OF THE LYMPHOCYTOSIS OF ACUTE INFECTIONS

By William E. Sanders, B.S., A.M., M.D., Des Moines, Iowa.

ONE of the most striking phenomena of the acute infectious diseases is the variation in the absolute number and the relative proportion of the different forms of the white blood cells as observed in the peripheral blood.

Such a study of the leucocyte count is now recognized as one of the most constant criteria for the differentiation of many of the acute febrile infections.

The most striking feature in such conditions, with perhaps the exceptions of lues, pertusses, and typhoid, is an absolute increase in the leucocytes and a relative increase in the polynuclear neutrophils.

Within the past few years a few cases of acute infective lymphocytosis, the nature of which is not at all well understood, have found their way into the literature.

Among these may be mentioned particularly the contributions of F. Marchand[1], and R. C. Cabot[2], the latter reporting five cases, in one of which the lymphocyte count reached as high as 86 per cent.

A critical study of some of the reported cases leaves one somewhat uncertain as to their true nature, and, indeed, it is not always possible to determine whether a given case should be classified as an acute lymphocytosis or an acute lymphatic leucemia as is so well brought out in some of the cases reported by Barker, Baetjer, and Miller[3].

The present paper reports a fatal case of Ludwig's Angina in which a remarkable, so-called, lymphocytosis was observed, and it is my purpose to use it as a basis for a possible criticism of the infective lymphocytoses.

CASE HISTORY

This concerned a young farmer twenty-six years of age, of good family and personal history, and who had just recently been accepted for life insurance, and whose illness began with symptoms resembling a cold in the early part of December, 1915.

About the last of the mouth he visited friends in Oklahoma and returned to his home in southern Iowa in January not feeling quite well and within a few weeks developed a sore mouth, with swelling and redness of the gums and marked salivation.

Notwithstanding the usual treatment for stomatitis the mouth failed to improve and by the middle of February he began to show a slight fever with swelling of the right submaxillary region.

After about two weeks this was opened by a deep incision, and a very little pus and blood secured which showed a diplococcus, thought to be the pneumococcus, and from which a vaccine was made.

He was treated with this vaccine for several weeks during which time the submaxillary swelling subsided and the stomatitis slightly improved.

About the first week of April a swelling rapidly developed under the left jaw and he was referred to me at the Iowa Methodist Hospital on the evening of April 10.

He was fat, but very pale, and had a swelling of woody hardness in the left floor of the mouth and under the left jaw, extending well onto the neck.

The mucous membranes were very pale and the gums so badly swollen as to almost conceal the free margins of the teeth and from which could be wiped away a thrush like exudate and a small amount of pus expressed from their dental margins.

The breath was remarkedly free from fetor, and there was considerable salivation.

The chest was negative except a soft systolic murmur over the cardiac apex, and the spleen was just palpable.

Neither sugar nor albumin was found in the urine.

Blood counts made on the twelfth, during which time the temperature ranged from 101° to 104.8° F., showed hemoglobin 65 per cent erythrocytes, 2,0000,000, slight anisocytosis, an occasional nucleated and a few stippled red cells.

The leucocyte count was 11,000, of which 96 per cent were classed as lymphocytes, mostly of the larger variety.

Almost daily examinations throughout the following week, at which time he died, showed essentially the same condition of the leucocytes, though the total count rose to 15,000 and on the day of death to 23,000.

Cultures from a very small amount of pus secured by radical operation of the submaxillary triangle on April 13 revealed pure cultures of *staphylococcus aureus.*

Blood cultures were not made.

During the last two days of illness swelling occurred in the deep cervical lymphatics of the right side, while the swelling of the left jaw extended to the soft palate, the left eye and the left upper chest.

There was severe, sudden pain in the left eye ball, and hemorrhages occurred from the nose, mouth, and bowels.

Within a few hours after death the body became markedly emphysematous, and at autopsy the internal organs showed the characteristic frothy appearance of *gas bacillus* infection.

Smears and sections from these organs showed this organism present in great numbers.

Without discussing the primary, or the secondary nature of the mouth infection, or the equally interesting relationship of the gas bacillus to the anemia[4], it is interesting to observe that the relative lymphocytosis here observed is greater than that hitherto reported.

Cabot reports 86 per cent in one of his cases, while this case showed 96 per cent.

Unfortunately the fresh slides were only studied with the Wright stain, while those which were preserved at the time were studied months later with Wright's, Giemsa's, and hematoxylin and eosin.

It is greatly to be regretted that these slides were not studied for the leucoprotease and peroxidase reactions, for without these the nature of those cells which we have taken for lymphocytes must remain somewhat questionable, notwithstanding that by the methods employed there was scarcely a question of their nature.

The almost constant and uniform nature of the dominant cell with a simple nucleus and a well developed ring of nongranular cytoplasm left little room for doubt that they were what we have all hitherto regarded as large lymphocytes.

About nine per cent of the total leucocytes are without question the small lymphocytes, and about an equal percentage no one would doubt as large lymphocytes, but these latter grade away insensibly into larger nongranular mononuclear cells which from their morphology and tinctorial properties every one who studied them looked upon as lymphocytes, but which after a more careful study, taken in connection with certain other hematological and clinical features of this case I am inclined to believe are susceptible of another interpretation.[5, 6, 7]

A study of 555 cells from various slides made at various times throughout the last week of illness showed only 13 with distinct neutrophilic granules, while the remaining 542 were classified as nongranular, the total numbers and percentages being as follows:

Nongranular Cells.	Total.....	97%.	
	Small nongranular lymphocytes,	51.....	9%.
	Large nongranular lymphocytes,	51.....	9%.
	Large nongranular mononuclears, (lymphocytes?)	424.....	77%.
	Transitional, (indented nongranulars)	6.....	1%.
	Polymorphonuclears, (nongranulars)	7.....	1%.
Neutrophile Granulars.	Total.....	3%.	
	Large slightly granular mononuclears (lymphocytes?)	8.....	1%.
	Polymorphonuclear granular (leucocytes)	5.....	1%.
	Eosinophiles and Basophiles	0.....	0%.

From the above table it is seen that about 95 per cent of the cells are mononuclear, nongranular leucocytes, apparently identical though in some instances slightly larger than the so-called large lymphocyte, and from the blood picture one would hardly hesitate to make the diagnosis of lymphocytosis or possibly lymphatic leucemia, though for the latter the total leucocyte count is very low.

It seemed impossible to conceive that lymphocytes could migrate into the cellular tissues of the floor of the mouth and neck in sufficient numbers to account for the extensive board-like swelling.

We therefore believe[8] that they are the immature histological antecedents of the granular myelocyte; viz., the nongranular myeloblast, and that future studies by the more recent methods will show the leucocyte of the infective lymphocytoses, and most likely the acute lymphoid leucemias to be of myeloid instead of lymphoid origin.

BIBLIOGRAPHY

[1]Marchand, F.: Lymphozytosen der Infectionkrankheiten, Arch. f. klin. Med., cx, Nos. 3-4.
[2]Cabot, R. C.: Lymphocytosis of Infections, Am. Jour. Med. Sc., cxlv, No. 3.
[3]Barker, Baetjer, and Miller: South. Med. Jour., Feb., 1916.
[4]Herter: Jour. Biol. Chem., Aug., 1906.
[5]McJunkin, F. A.; Studies in the Mononuclear Cells of the Blood, Arch. Int. Med., xxi, No. 1.
[6]Luden, G.: Studies in Cholesterol, Jour. Lab. and Clin. Med., iii, No. 3.
[7]Monographic Medicine, iii.
[8]Sanders, W. E.: Pathology and Diagnosis of the Hemopoietic System, Iowa Med. Soc., 1918.

SOME NOTES CONCERNING HEMOLYTIC STREPTOCOCCUS INFECTION*

By Moyer S. Fleisher, Captain, M.R.C., and C. D. Hamilton, First Lieutenant, M. R. C.

DURING the latter part of March and early part of April, 1918, there occurred at Camp Wadsworth an epidemic of measles and practically concomitant with it an epidemic form of bronchopneumonia associated with empyema.† During this time there were some 200 cases of measles, and 21 cases of bronchopneumonia or empyema in which a hemolytic streptococcus was the causative agent.

In the main the characteristics of this epidemic were similar to those noted in other camps. The number of cases occurring here, however, was not very large, and the infection with the hemolytic streptococcus was confined very largely to the men of two organizations (1st Pioneer Infantry, and 2nd Pioneer Infantry).

Of the 21 cases of bronchopneumonia and empyema, 8 were among men in the 1st Pioneer Infantry, 7 were in the 2nd Pioneer Infantry. The men affected were chiefly men who had recently arrived at this camp and were individuals from sparsely settled districts who were in their organizations brought into contact with men who had been in camp for some time and who came originally from larger cities. It is also interesting to note that two regiments were quartered alongside each other. The other 6 cases were distributed among other organizations. It also seems that in the cases occurring in this camp there was less of a tendency towards the development of metastatic lesions than had been observed at some other camps.

At the same time that this small epidemic existed, a number of other cases of pneumonia occurred, largely, however, of infection due to a Type 4 pneumococcus. As the infections with the hemolytic streptococcus subsided, there was noted a marked increase in the number of pneumonias due to a nonhemolytic streptococcus. This is best seen in the table showing the cases typed for pneumococcus during the months of April and May.

Table I

	APRIL		MAY	
	SPUTUM	PLEURAL FLUID	SPUTUM	PLEURAL FLUID
Type I	5	1	2	1
Type II	4	0	0	0
Type III	6	2	0	0
Type IV	34	6	2	0
Hemolytic Streptococcus	13	11	2	0
Nonhemolytic Streptococcus	3	4	22	9
Negative	0	6	0	8

The interesting facts presented by this table are, first, that the infections

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†There were also at this time a considerable number of infections of the upper respiratory tract being admitted to the Base Hospital which were probably due to hemolytic streptococcus infections.

with hemolytic streptococci disappeared almost entirely in the month of May, but that in the place of the hemolytic streptococcus there appeared a nonhemolytic streptococcus which was the most important causative agent in the pneumonias occurring during the month of May. Infections with the nonhemolytic streptococcus began to appear in the latter part of April, and concomitantly the infections with hemolytic streptococci fell off in frequency.

It is not our intention to dwell upon any of the aspects of the epidemic of bronchopneumonia and empyema, as it presented, at least from the bacteriologic point of view, but little difference from the conditions noted at other camps. Suffice it to say that in nearly all cases in which hemolytic streptococci were found in the sputum, the same organisms were also found in the pleural exudate. At autopsy, conditions very similar to that described by McCallum as being found at Fort Sam Houston during the epidemic there were seen. Blood cultures during life were negative and the only blood culture which was positive for hemolytic streptococci was taken within twenty-four hours of death, and after the individual had had a resection of a rib done. Culture from the lungs and from the heart's blood after death showed hemolytic streptococci in all cases which were so cultured.

The one aspect of this rather short-lived epidemic upon which we wish to dwell is the occurrence of hemolytic streptococci among the troops of this camp during and after the epidemic. During the latter part of the epidemic and for some time afterwards, we made a survey for hemolytic streptococci of the patients entering the Base Hospital and the patients in the wards of the hospital, which, while not quite as extensive or as exhaustive as we should have liked, does furnish us some rather interesting data.

A first suggestive sign was noted some time before the epidemic appeared. During the latter part of March and early part of April a large number of throat cultures were taken for the detection of meningococcus carriers, these being taken in the 1st Pioneer Infantry, when it was observed that a very large number of these plates showed small colonies about which there was distinct hemolysis. While no examination was made of these colonies to determine whether they were hemolytic streptococci it seems that probably they were and that we had here the primary focus from which the organisms which were later the cause of the epidemic were spread. It should be borne in mind that it was particularly in this regiment that the measles and a large percentage of the hemolytic streptococcus pulmonary infections arose. It was in the regiment quartered in the adjoining quarters that the next largest number of hemolytic streptococcus infections arose.

When the nature of the epidemic was actually noted, a survey was begun of cases admitted to the hospital, of selected suspicious cases and of certain wards in the hospital to detect the presence of hemolytic streptococci in the throats of the patients. As the epidemic was rather short-lived and disappeared rather shortly after its nature was appreciated, our results are not very extensive or as full as we should have liked them to be; nevertheless, we believe that they point in the direction of certain interesting facts.

During the month of April throat cultures were taken from 203 individuals and were examined for hemolytic streptococci, of which 86 were posi-

tive—42 per cent. During the month of May, when the infections with hemolytic streptococci had practically disappeared, a total of 230 were examined and of these only 22 showed hemolytic streptococci—9.5 per cent. These 22 positive cases were noted in the cultures taken in the early part of May and during the latter part of the month only one positive culture for hemolytic streptococci was obtained. The figures just mentioned represent figures for cases admitted, especially selected cases and various wards in the hospitals.

Cultures were taken from cases admitted to the hospital from April 23 on; both medical and surgical admissions were examined: this was done so that we would have cases of a general type and not only medical cases which might possibly represent chiefly cases of tonsillitis, or pharyngitis.

TABLE II

CULTURES AND ADMISSIONS FOR HEMOLYTIC STREPTOCOCCI

	APRIL 2-30		MAY 1-31	
MEDICAL CASES	Total	30	Total	6
	Positive	7	Positive	0
SURGICAL CASES	Total	23	Total	40
	Positive	12	Positive	0
ALL CASES	Total	53	Total	46
	Positive	19	Positive	0

The very marked difference between the cultures taken in April and those taken in May is evident, and it appears that a disappearance of hemolytic streptococci took place about the end of April.

During the latter part of April and early part of May throat cultures were taken from a number of medical cases in which it was suspected that hemolytic streptococci might be present. This was done as a precautionary measure for purposes of isolation of such cases and in order to treat such cases to rid them of the organisms. Between April 23 and April 30, 20 individuals were cultured and 7 were positive. After April 30, 20 more were cultured and only 3 were positive. These figures correspond to a certain extent with the figures noted in the cultures of admitted cases; it should be mentioned that the cultures of selected cases were taken only during the early part of May while the cultures from admissions were taken at various periods throughout the month.

WARD INFECTIONS

In the article by Cole and McCallum it is suggested that the hemolytic streptococci are spread to individuals by transmission while the patients are in the wards. This statement is based upon repeated cultures taken of individuals in measles wards, and it is shown that the longer the individuals are in the wards, the greater the number of individuals showing hemolytic streptococci.

We have not carried out similar examinations, but have in some cases taken cultures from the individuals in certain wards previous to admissions of carriers of hemolytic streptococci to that ward, and have again cultured the

individuals in the ward some time after the admission of the carriers. We have also made several examinations of certain wards. Our results do not seem to point to the fact that ward infection does take place under the conditions existing in general medical wards or in pneumonia wards. We can not, however, give any evidence concerning the possibility of ward infections in measles wards as our investigations do not admit of any conclusions regarding these wards.

On April 22 a positive carrier of hemolytic streptococci was admitted to one of the general medical wards; three days later all the patients in this ward were cultured and only this one individual was found to be positive. It is of course possible that the time elapsing between the introduction of this positive carrier into the ward and the culturing of the entire ward was too short for infection to take place; however, within three days Cole and McCallum noted a marked increase in the percentage of individuals positive for hemolytic streptococci in the measles ward which they examined.

On April 25 the patients in another ward were all cultured and 3 out of 29 were positive for hemolytic streptococci. On April 29 another individual with hemolytic streptococci was admitted to this ward; four days after this last-named individual was admitted, the entire ward was again cultured and only one individual was found to be positive for hemolytic streptococci.

On April 25 a patient in the lobar pneumonia ward was found to have hemolytic streptococci in his throat. The entire ward was cultured three days later and out of 30 individuals only this one man was positive; two more positive carriers were brought to this ward on April 29 and four days later the entire ward was cultured and these original three were the only ones who had hemolytic streptococci in their throats.

Somewhat similar results were noted in still another ward. In no case was there any evidence whatsoever that the introduction of individuals who were carriers of hemolytic streptococci into a ward had any effect in spreading the infection with this organism to the other individuals in the ward; and so-called "ward infection" does not seem to have taken place.

THE RELATION BETWEEN MEASLES AND HEMOLYTIC STREPTOCOCCI

The presence of hemolytic streptococci in the throats of individuals affected with measles has come to be pretty widely accepted. At the time that the measles epidemic first appeared in Camp Wadsworth, the men affected came very largely from one organization (1st Pioneer Infantry) although the other individuals affected with measles were pretty widely scattered so far as concerns organizations. Cultures were made, the last days of April, of the throats of all individuals in two measles wards, and of the 35 individuals cultured 23 showed hemolytic streptococci. In these wards somewhat more than 50 per cent of the individuals came from the 1st Pioneer Infantry. Mumps was also epidemic at this time, and was especially prevalent in the same organization; we took cultures in the mumps ward at about the same time that we cultured the measles ward, and here out of 35 men 18 were positive for hemolytic streptococci. There would appear from the figures above to be some relation between measles and hemolytic streptococci, but certainly not a specific

relation, since the percentage of positive carriers among the individuals affected with mumps was quite as high as among the patients with measles.

During the latter part of May a number of cultures were taken of the patients at that time in the measles wards, and of 61 individuals cultured, none showed hemolytic streptococci. These men were chiefly if not entirely individuals from different organizations from those which had been affected with measles in the previous month and had but recently come to the camp. There seems here to be definite evidence that there is no connection between measles and hemolytic streptococci; and that the previous findings of the prevalence of hemolytic streptococci among measles cases was only chance.

DISCUSSION

It appears from facts gathered during and after a mild epidemic of bronchopneumonia associated with empyema in which the streptococcus hemolyticus was the principal organism, that at the time of this epidemic and probably preceding the appearance of the epidemic there was a large number of carriers of hemolytic streptococci present in the camp. A majority of the cases of bronchopneumonia and empyema occurred in the organization in which it is probable that numerous carriers were present. However, even in patients in the hospital in whom hemolytic streptococci were found in the throat we did not see the development of the streptococcus empyema syndrome; so that it is evident that factors other than the presence of hemolytic streptococci are of importance in the development of this condition. What this may be we can not state. Fox and Hamburger dwell at length in their articles upon the several factors which might be of importance in development of the disease. It is unfortunate that we do not know whether these men who were so severely affected by this condition became infected here or were already affected before they arrived at camp; it is, however, probable that they were carriers before they arrived at Camp Wadsworth. They came to this camp about the middle or the latter part of March and within a few days after their arrival here the organization was cultured for meningococcus carriers, at which time as previously stated they showed apparently a large number of positive hemolytic streptococcus carriers. It is of course possible that they may have been infected before their arrival at Camp Wadsworth, but the fact remains that the streptococci if they were present at the end of March did not become virulent until some two weeks later. Possibly they were gradually acquiring increasing virulence as Fox and Hamburger have suggested.

It has been shown above that ward infection with hemolytic streptococci did not take place here during the height of infection with hemolytic streptococcus. It is possible that under different conditions and dealing with a more virulent infection or possibly with men under different conditions such infections in wards may occur, but it can not be accepted that it does occur as a general thing.

It has also been shown that hemolytic streptococci are not constantly to be found in the throats of individuals suffering with measles, and it would appear that the occurrence of the measles and the streptococcus infections at the same time was simply chance.

LABORATORY METHODS

THE SPINAL FLUID IN EPILEPSY: A PRELIMINARY REPORT*

By John H. Larkin, M.D., and Leon H. Cornwall, M.D.,
New York City

THE bloods and spinal fluids of 146 cases of epilepsy were submitted to routine examinations, consisting of the Wassermann reaction upon each and on the spinal fluids pressure estimations, cell counts, globulin and colloidal gold reactions.

In the bloods the Wassermann reaction was positive twelve times (9 per cent). *Post hoc propter hoc* an etiologic relationship between syphilis and the epilepsy might be presumed to exist in those cases. No such conclusion, however, will be ventured until the associated clinical analyses have been completed, but the incomplete clinical investigation, which includes a search for the evidences of stigmata of congenital lues, indicates to us that there is a causal relation between the two diseases in a much higher percentage of cases.

Diffuse neurosyphilis was present twice and general paresis once. The Wassermann was positive in the spinal fluid in one case of neurosyphilis and in the case of paresis, but in none of the other fluids.

Pressure estimations were made fifty-nine times, of which nine were diminished (15 per cent), 18 were increased (31 per cent), and 32 were normal (54 per cent). The blood Wassermann was positive in one of the nine cases with diminished fluid pressures, and in two of the 18 cases with increased fluid pressure.

Among 143 fluids on which cell counts were made, a pleocytosis was present but once, in a fluid from one of the cases of diffuse neurosyphilis. Six cells were present in two and four cells in five fluids. Twenty-six fluids were acellular and the remainder contained from one to three cells per cm.

The globulin content was tested in 137 fluids. There was a definite increase in 7 (5 per cent) and a slight excess in 22 (14 per cent) with the Ross-Jones modification of the Nonne Phase I reaction. Two of the fluids with a slight excess of globulin came from positive blood Wassermann cases, but none of the fluids with definite globulin increase came from cases with positive blood Wassermanns.

Of all the spinal fluid reactions only the Lange colloidal gold test showed any considerable deviation from the normal. This test was applied 114 times. Fifty-three (46 per cent) were within normal limits. Fifty-two (46 per cent) gave low curves to 2. Eight (7 per cent) gave moderately high curves to 3. The one paretic fluid gave the usual Type I or paretic curve. All but two of the fluids from positive serum Wassermann cases gave reactions within the

*From the Pathologic Laboratories of the New York City Hospital.

normal limits. In the two exceptions the curves only went to the shades of decolorization represented by the number 2.

With our present crude methods of studying the chemistry of the spinal fluid there appear to be certain similarities in the effect produced by this secretion on solutions of colloidal gold in epilepsy, nephritis and vascular lesions of the neurospinal axis; in diffuse neurosyphilis and anterior poliomyelitis, and in paresis, multiple sclerosis, lateral sclerosis, brain tumor and eclampsia.

Is epilepsy due to some chemical change in the blood increasing its toxicity and thereby inducing the characteristic explosive motor phenomena after the threshold of tolerance is exceeded? Or are the objective phenomena induced by an increased toxicity of the spinal fluid caused by an altered physiology of the cells of the chorioid plexus, meninges or neural parenchyma?

These questions remain to be answered. Chemical studies of the blood and spinal fluid in epilepsy offer a fruitful field for further investigation.

Colloidal chemistry may furnish a key to the explanation of some of these questions.

METHOD FOR OBTAINING MOUSE BLOOD*

By Holland N. Stevenson, M.D., New York City

THE usual method of obtaining mouse blood for tissue culture has been to take it from the carotid artery. In such a small animal this is a rather difficult technical procedure, and introduces not only a large time factor but also a strong possibility of contaminating the blood with tissue juices. These difficulties have greatly reduced the possibility of *in vitro* work with mouse tissues on any very large scale.

In searching for a method of obtaining mouse blood which would obviate these difficulties, it was found that the intracardiac method of obtaining blood which has been applied to larger animals could be applied to mice with a large measure of success. The object of this paper is to present this application of the method as it has been developed at the laboratory of the Crocker Fund, where it has proved its value during an extensive study of the growth of mouse tissue in homologous plasma.

Syringe.—The type of syringe employed was the 2 c.c. Luer, graduated in 0.1 c.c. The needles were number 22, 1¼ inches long. It was necessary to have a needle with a sharp point, in order that the operation be successful. Two of these needles were wrapped in cloth with the syringe and sterilized by steam. A number of these packages were always kept in the ice box ready for use.

Animal.—The hair was removed from the anterior portion of the thorax. The mouse was etherized and tied out on the animal board. Great care was taken that the forelegs were rather tightly stretched and arranged at an angle of about 60° with the longitudinal axis of the body. The skin was then thoroughly washed with 95 per cent alcohol.

*From Columbia University, George Crocker Special Research Fund, F. C. Wood, Director.

The syringe and needle were thoroughly rinsed with ice-cold olive oil to prevent clotting. The point of inserting the needle varied slightly with the size and position of the animal; usually it was in the third or fourth right intercostal space at a point somewhere between the right border of the sternum and the mammary line. The direction in which the needle was pointed was often determined by the visible pulsation of the heart. This usually became quite apparent when the needle was pressed gently upon the thorax producing a slight depression. Often after the needle had been inserted and had come in contact with the heart, one could feel its pulsations provided the syringe was not held too tightly.

After the needle had been inserted to a distance which should bring it into the heart, a moderate suction was created in the syringe. In a large percentage of instances the blood immediately flowed into the syringe. If this did not occur, the suction was maintained and the needle very slowly advanced and if blood was then not obtained, the needle was very slowly withdrawn. If the blood still did not flow, the needle was withdrawn practically to the surface and its direction changed until the desired result was obtained.

After the blood began to flow, it was essential to hold the syringe absolutely still, for the slightest movement dislodged the point and the operation was unsuccessful.

The amount of blood obtained from one mouse was from 0.5 to 1.25 c.c. The usual amount was 0.75 c.c. The mice did not always die from the operation and many were bled twice, some even three times. The blood obtained in this way yielded plasma which would often remain without clotting for two and one-half hours.

MODIFICATION OF GRAM'S STAIN FOR POSITIVE BACTERIA*

By Joseph Leidy (Philadelphia), Captain, M. C., U. S. A.

IN the course of some experiments in staining bacteria according to Gram's method it was found that any of the metallic iodides soluble in water may be substituted for the potassium iodide in Gram's Iodine solution. With the iodides of magnesium, soda, arsenic, aluminum, zinc, iron, both ferrous and ferric, an equally satisfactory result was obtained as with potassium. The iodine dissolves more slowly with ferric iodide and arsenious iodide than with the others, which, however, is not objectionable.

In the case of the ferrous iodide and arsenic iodide, we thought the stain was rendered a deeper hue. This after many trials. As with most microscopic technic, care should be exercised to follow all details.

At the present time, when the cost of the potassium salts is to be considered, the cheapness of some of the others, such as arsenic and ferrous iodide, is worthy of consideration when large quantities may be necessary for laboratory use in class demonstration. The modification is not without value.

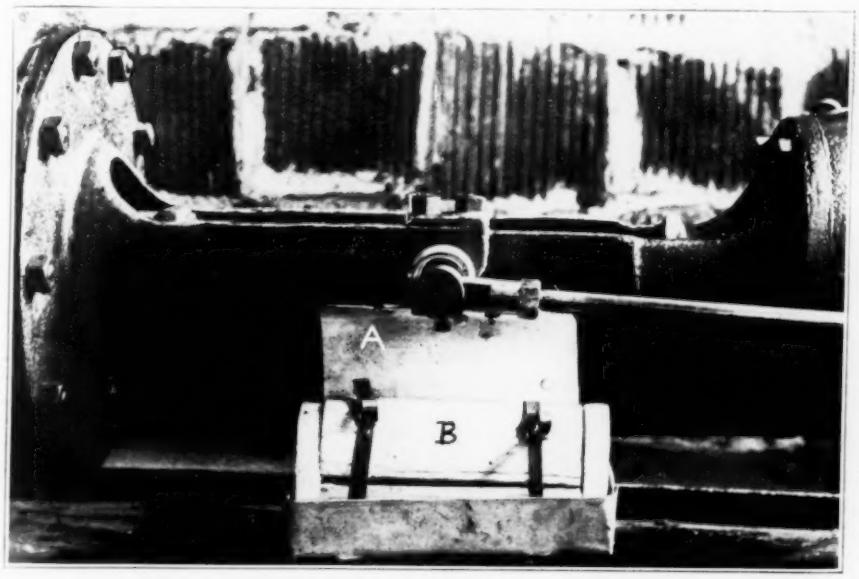
*From the Chemical Warfare Service, Brady Laboratory, New Haven, Conn. Authority to publish granted by the Surgeon-General's Office.

A SIMPLE SHAKING APPARATUS

By A. L. Garbat, M.D. (New York City)
Captain, M.C., U. S. Army; Chief of Laboratory, General Hospital No. 12, Biltmore, N. C.

THE only essential is a pump, the piston of which works in a to and fro movement. At our institution, the vacuum pump for the radiator system was found suitable. As is seen in the photograph, the apparatus consists of two parts, (A) a cradle made of metallic sheet iron which is tightly fastened to the side arm of the piston, and (B) the container which consists of a cylindrical block of wood hollowed out in the center and split in half, into which the bottle for shaking is placed.

The containers provided by the Army Medical School for the shipment of bacteriologic material also serve this purpose well. The container is strapped tightly to the cradle. The to and fro action of the piston provides an efficient motion for shaking.



DRAWING FOR AUTOPSY TABLE CONSTRUCTED BY ENLISTED MEN FROM "LEFT OVER" LUMBER*

Reported by Major Fred W. Baeslack, M.C., U. S. A.†

I HAVE thought that it might be worth while to make available for the medical profession the accompanying drawing for an autopsy table constructed by members of the enlisted personnel from "left-over" lumber.

*Published by permission of the Surgeon General.
†From U. S. Debarkation Hospital No. 2, Staten Island, N. Y.

The 12″x12″ sink, the drain connection and metal sheeting, costing from twelve to fifteen dollars, constitutes the entire cash outlay for its construction.

The water is supplied, both cold and hot, from connections above the table, through six feet of rubber garden hose.

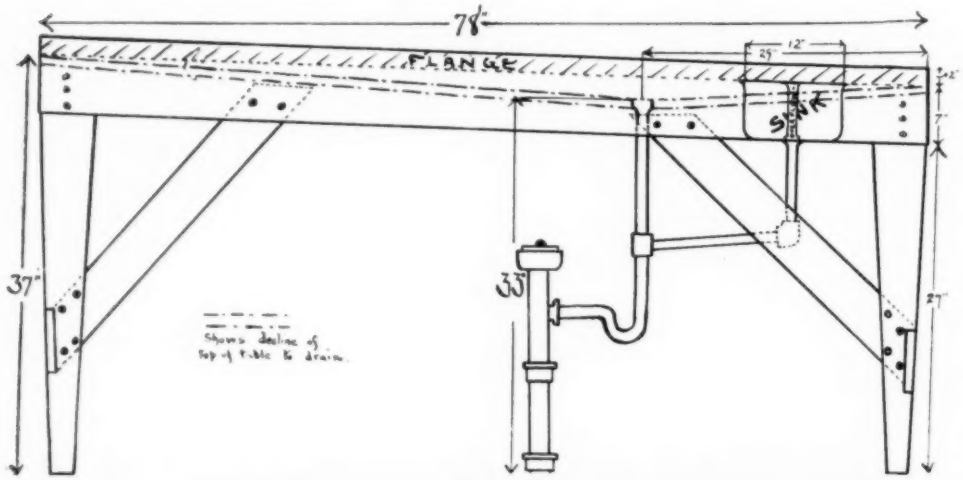


Fig. 1.

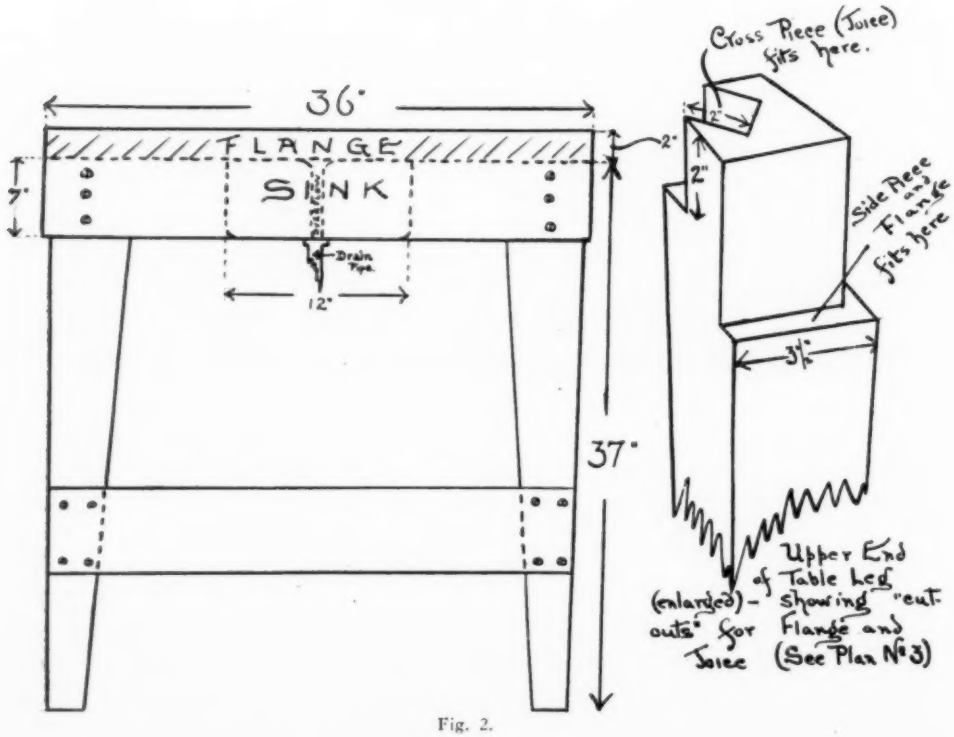


Fig. 2.

The advantages of this table are:

(a) The sanitary construction.

(b) The sink near the foot of the table permits the washing of organs removed at autopsy, and obviates working with soiled hands and instruments.

The accompanying drawings will need no further explanation.

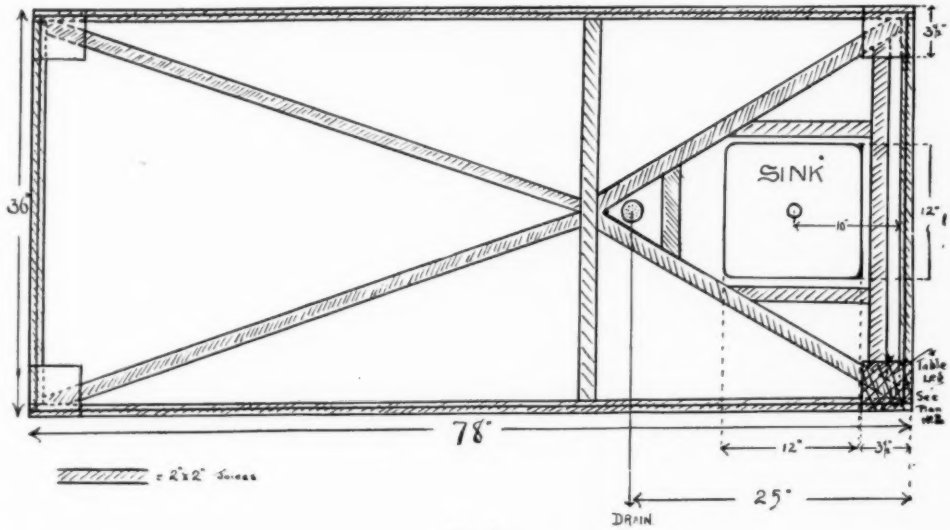


Fig. 3.

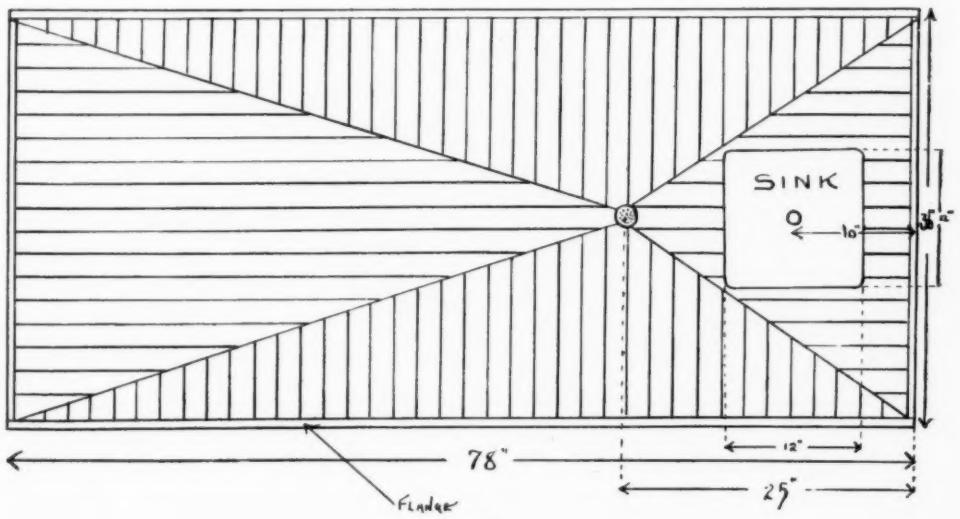


Fig. 4.

A SIMPLE AUTOMATIC KEY FOR USE IN THE STUDENT PHYSIOLOGIC LABORATORY*

By S. Morgulis, Ph.D., Omaha, Neb.

IT is often desirable in experiments performed by students in the physiologic laboratory to employ a key that would permit to make or break the electrical circuit automatically and at exactly the same point. By superimposing a series of curves the effect of various factors is best illustrated since the details of the different curves are thus readily compared. In this laboratory we have used an arrangement which for extreme simplicity and cheapness is most suitable for student work. Furthermore, it has the advantage that each student can make this himself. We used this method for the past three years with considerable success, and in publishing this suggestion we are prompted by a feeling that others may perhaps also find it useful.

The key consists merely of a piece of stout copper wire (No. 18) wound about the screw of a Harvard kymograph by which the sleeve of the drum bears on the steel shaft. It is fastened in position by the set screw. A metal rod (also made by the Harvard Apparatus Company) is clamped in the stand bearing the signal magnet as well as the muscle holder and lever. The rod should be directly above the kymograph and should extend an inch or two beyond the circumference of the drum. As the drum moves, the circuit is closed and opened each time the copper wire glides over the rod. A series of muscular contractions may be recorded in succession, the contractions all rising from the same point on the surface of the kymograph.

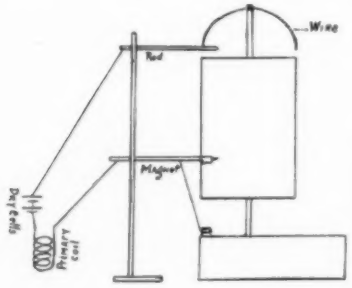


Fig. 1.

The copper wire can be made with two arms, and in this way a double record will be secured for each revolution of the drum; but three or four similar records can be prepared just as easily. As our students work in groups of two, a piece of wire bent in the shape of a semicircle—twisted in the middle to form an eye—is fastened under the set screw, and all records are thus made in duplicate.

The method is so simple that our students with a short experience in the physiologic laboratory get excellent results. I am reproducing records recently obtained by the students, one showing the effect of temperature, the other of fatigue, on muscular contraction (see Figs. 2 and 3).

Of course, the wire must be so adjusted that, as it goes round with the drum, its free ends just barely touch the rod. This is very easily accomplished, securing perfect contact without undue friction which would otherwise interfere with the free movement of the kymograph. Although this key both makes and breaks the circuit, in practice these follow each other with such

*From the Department of Biochemistry and Physiology, Medical College, Creighton University, Omaha, Neb.

rapidity that only a single response of the muscle results. To complete the primary circuit, one lead from the batteries is attached to the rod, while the other lead is fastened to the milled head on the kymograph base which regulated the fast speed. A signal magnet is generally included in the primary

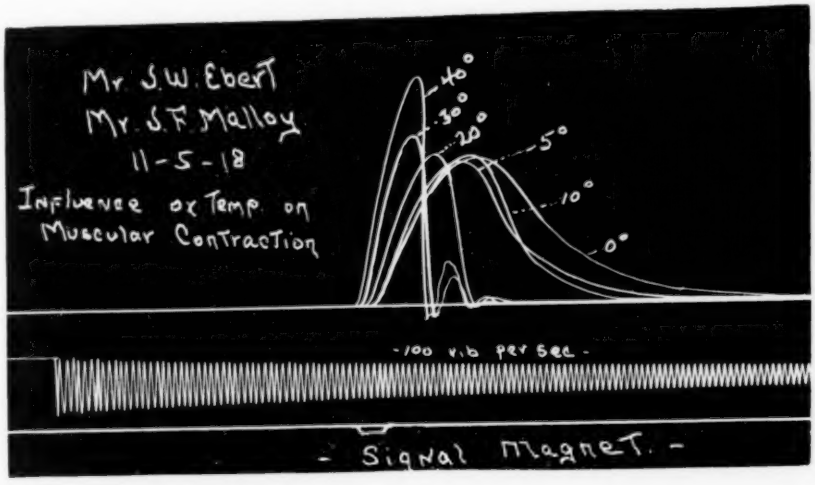


Fig. 2.

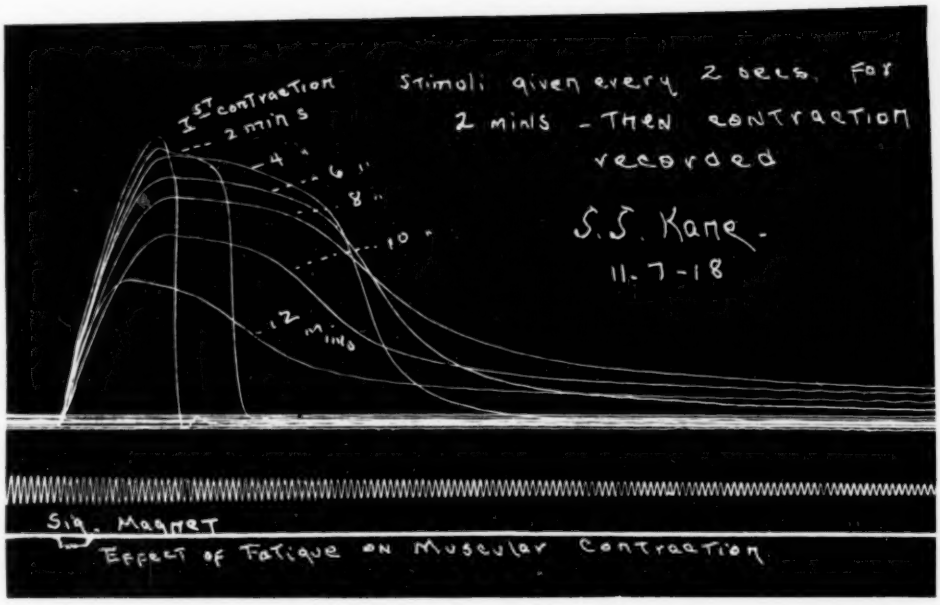


Fig. 3.

circuit. While this method is susceptible of further improvement, the high degree of satisfactoriness of the results does not seem to justify the introduction of other modifications in view of the expense which would be involved.

A TYPE OF SIMPLE KEY FOR LABORATORY USE*

By John A. Higgins, Chicago, Ill.

AN important factor in the physiologic and pharmacologic laboratories is the use of some type of a simple electric key. There are a great number of simple keys already on the market, but the majority of these keys seem to receive more or less criticism regarding their laboratory value. The spring type of a simple key, a type which is best illustrated by Jackson,† is quite often criticized where a continuous electric stimulus is desired. The inability of such type of keys to remain closed during continuous stimulus, without constant pressure on the spring in order to make contact, seems to be the main drawback. When interrupted stimulus is desired, the knife switch type of simple electric keys quite often meets with disapproval because of their inability to break contact in as simple a way as can be had with a spring type of key.

Where these various types of simple electric keys have met with disfavor,

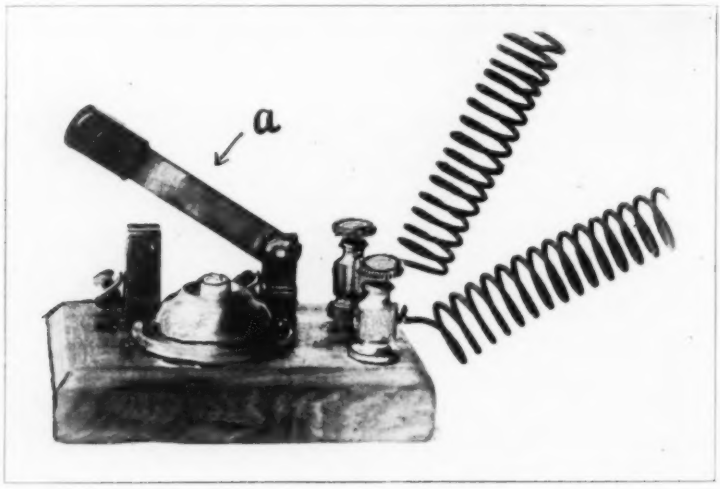


Fig. 1.

it is not uncommon to see the laboratory worker resort to the more expensive telegraph type of key. The telegraph type of key is generally so constructed that for continuous stimulus the key can be closed, without further attention, for any definite period of time, whereas for interrupted stimulus the key can be so adjusted as to give interruptions as often as desired by simple pressure on a knob and for each interrupted stimulus.

The cost of the telegraph key, however, retards its greater use and especially so in the student laboratories. I have therefore devised a key which is inexpensive, yet effective, and can be used to advantage among students as well as research workers. It (Fig. 1) is constructed by mounting on some suitable

*From the Department of Physiology, University of Illinois School of Medicine, Chicago, Ill.

†Jackson, D. E.: Experimental Pharmacology, C. V. Mosby Co., p. 145.

base, and connecting in parallel, a single knife switch key together with an electric door bell push button, two binding posts being used as terminals.

While the material used in the construction of this key has cost me approximately thirty-one cents, which is within the cost of the average laboratory simple key, yet I have a key which is just as effective in the laboratory as the more expensive type of telegraph key. A continuous stimulus while in circuit with an inductorium and electric cell, can be had by closing the single knife switch lever at *A*. The interrupted stimulus can also be received, with the use of the same key, by opening the single knife switch lever and making interruptions with the aid of the door bell push button.

A TYPE OF STIMULATING ELECTRODE*

By John A. Higgins, Chicago, Ill.

A LARGE assortment of stimulating electrodes for use among the medical students, as well as for use among the laboratory research workers, are illustrated as a rule in the different physiologic text books and laboratory manuals. Sanderson,[1] Stirling,[2] Porter,[3] Howell,[4] Jackson,[5] etc., illustrate one or more of this large assortment of available types of electrodes.

A great majority of the stimulating electrodes generally terminate with projecting platinum points soldered to insulated copper wire. While the platinum has a higher resistance than copper towards electric energy still the platinum points are here added owing to its resistance against corrosion, therefore insuring a more perfect stimulus. Jackson,[5] however, has substituted German silver in place of the platinum points without any noted disadvantage.

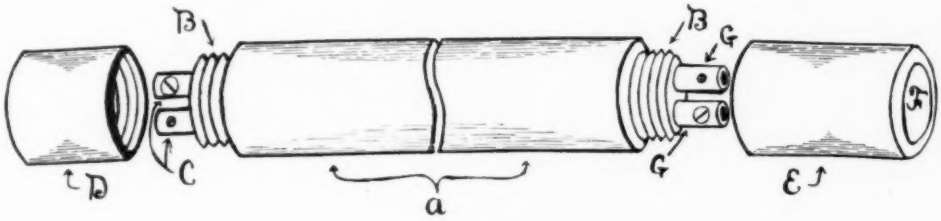


Fig. 1.

While students or other laboratory workers may have success in the handling of electrodes, still it is not uncommon to see platinum points broken off at the soldered connection. When the platinum points break off it necessitates more or less skill and time in resoldering the points into place for future service.

Endeavoring to overcome any disadvantages, as may occur in the older types of stimulating electrodes, I have accordingly designed a new type (Fig. 1). The advantages offered in this new type are first the elimination of platinum points, substituting other inexpensive metals and yet insuring a good electric

*From the Department of Physiology, University of Illinois School of Medicine, Chicago, Ill.

contact on a nerve or other body tissue; second, the advantage of bringing into laboratory services discarded steel phonograph needles, which, no doubt, are plentiful and can be of service until corrosion sets in; lastly, such changes as are deemed advisable can be easily and quickly made by a student or research worker before or during an experiment and without the skill of resoldering connections.

The stimulating electrode as illustrated is constructed from a piece of round, hard rubber rod (*A*) $\frac{3}{8}$ inch thick by 3 inches long. On each end at *B* was cut away approximately $\frac{1}{16}$ of an inch and threads numbering 32 to the inch were then cut upon the remaining ends. Two holes, using a $\frac{3}{32}$ inch drill, were drilled from end to end in the hard rubber rod, allowing approximately $\frac{3}{64}$ of an inch between each drilled hole. Two pieces of $\frac{3}{32}$ by $3\frac{3}{4}$-inch brass tubing (*C*) were inserted into the drilled holes of the rubber rod. On each end of these brass tubes holes were drilled and threaded to accommodate 2/56 or smaller size screws. Caps were then made for each end of the rubber rod. The cap on the end which was designed to hold the projecting stimulating points (*D*) need only be long enough to act as a shield for the screw connections (*C*). Both ends of this cap should be fully opened. The cap towards the end of the rod, and to which are fastened the wires from the inductorium, is somewhat longer (*E*), but at one end the opening is only large enough to permit the positive and negative insulated wires to pass through snugly. These caps were made of hard rubber but it might be much easier to substitute metal caps, care being taken to avoid the metal caps coming into contact with the screw heads, etc., on the ends of the brass tubes.

In connecting up the electrode, pass the wires from the inductorium through cap *E* at point *F* and fasten to the ends of the brass tubes at *G*. Screw the cap onto the end of the rubber rod after making contact connections. On the ends of the brass tubes at *C* fasten in uncorroded steel phonograph needles or some similar inexpensive metal and cover up the contact connections with cap (*D*). The electrode is now ready for stimulations. If corrosion sets in on the projecting points from day to day, it will be found an easy procedure to remove cap *D*, replace the projecting points, and rescrew cap *D* into place. Hard rubber material for such electrodes can be supplied by the American Hard Rubber Co., 337 West Madison Street, Chicago, Ill.

BIBLIOGRAPHY

[1]Sanderson, J. B.: Handbook for the Physiological Laboratory, ii, Plate LXXXIX, Fig. 225.
[2]Stirling, Wm.: Practical Physiology, ed. 2, p. 157, Fig. 89.
[3]Porter, Wm. T.: Introduction to Physiology, University Press, Cambridge, Mass., p. 31, Fig. 9.
[4]Howell, Wm. H.: Text Book of Physiology, ed. 6, W. B. Saunders Co., p. 86, Fig. 29.
[5]Jackson, D. E.: Experimental Pharmacology, C. V. Mosby Co., p. 65.

MODIFICATIONS OF HENDERSON'S METHOD OF ESTIMATION OF THE HYDROGEN-ION CONCENTRATION OF URINE*

By Howard D. Haskins, M.D., Portland, Oregon

HENDERSON'S[1] method has made it feasible for any careful worker to estimate the true acidity of the urine. This method has been indispensable to the successful accomplishment of several important researches.

There is, however, a difficulty which has undoubtedly deterred many from using the method, namely, that the standards for comparison must be freshly prepared each day that estimations are made. After having had this problem in mind for several years, I have succeeded in preparing artificial standards that retain their proper color value for many months, and that are easily made up anew.

With the modifications proposed in this paper the method can easily be used by any clinician, and furthermore, with very little expenditure of time.

The excretion of strongly acid urine persistently day after day and at all times of day is undoubtedly often of clinical significance. It may furnish a clue to the existence of acidosis or a cardiorenal difficulty, or of some other condition well worth investigation. We are strongly of the opinion that not nearly enough use has been made clinically of the method. The estimation might well be made part of the regular urine examination when a case first comes under observation. Furthermore, it is indispensable in connection with the *alkali retention*[2] test for acidosis. In carrying out this valuable test litmus paper should not be depended on to determine when the urine has become alkaline. The bicarbonate should be administered at regular intervals until the urine comes to a definite H-ion concentration (e.g., P_H 7.4), following the example of Palmer and Van Slyke.[3]

MODIFICATIONS OF HENDERSON'S METHOD

1. *Indicators.*—We have realized for a long time that it is desirable to use only indicators that give a good gradation of red colors. Therefore the use of paranitrophenol was discontinued. Sodium alizarin sulphonate, recommended by Palmer and Henderson[4] did not seem at all satisfactory for our purpose. Rosolic acid was adopted for the range of acidities formerly determined with paranitrophenol.

By using methyl red, neutral red and rosolic acid as indicators, gradations from red to yellow throughout the entire series of the P_H standards are secured. One who is not at all expert can easily detect the difference in color of neighboring standards at every point in the series. With these colors it is easy to make the estimation by artificial light preferably using the new daylight lamp (Peerless Mazda C2).

2. *Acidity Standards.*—For some years we have preferred to use Sörensen's phosphate mixtures for all of the standards (and in the proportions recommended by Sörensen) instead of the mixtures suggested by Henderson. They are much more convenient, and probably more reliable.

*From the Department of Biochemistry, Medical School, University of Oregon.

3. *Use of Bottles.*—In carrying out Henderson's method we soon found that making colorimetric comparison of solutions in flasks was unsatisfactory, so that we adopted the use of French square bottles, the wide-mouth two-ounce colorless bottle being our final choice.

4. *Quantities Used.*—We have reduced the amount of distilled water used in an estimation to 20 c.c. and the amount of urine to 1 c.c. or less. Exactly 1 c.c. of indicator is taken in every case. The water is measured quickly with a graduate.

5. *Distilled Water.*—For research accuracy we found it necessary to use boiled distilled water. For rapid cooling of the water large heavy-walled pyrex test tubes are used. The water is poured into the tube boiling hot, a rubber stopper is inserted and while pressing this down the air is allowed to escape by prying one side of the stopper with a knife blade. The tube can be put into the coldest tap water at once, and the cooling takes but a few minutes. For ordinary routine work unboiled water can be used, but it should be put into a pyrex or nonsol flask when freshly distilled, and the flask must be kept sealed with a rubber stopper *constantly* except when water is being poured out. Distilled water kept in a bottle dissolves alkali from the glass.

Do not allow expired air to get into the flask. Excess of carbon dioxide in the water can change the estimation noticeably in the case of urines that are alkaline or very slightly acid.

6. *Permanent Standards.*—The artificial standards prepared by us to imitate the colors given by the Sörensen phosphate mixtures after the addition of the indicators, are made by adding amaranth and paranitrophenol in various proportions to a buffer mixture which contains KH_2PO_4 and K_2HPO_4, each being in one-tenth molar concentration.

The buffer solution (P_H 6.8) prevents the trace of alkali which gradually dissolves out of the glass of the bottles from changing the color of the standards. This solution gives a decided yellow collor when paranitrophenol is added, the intensity of the color depending on the amount of paranitrophenol used. Amaranth imparts a brilliant red color, and is not affected by the phosphate.

The amaranth and paranitrophenol solutions should be kept in pyrex or nonsol flasks. They do not fade when exposed to diffused light of moderate intensity.

The permanent standards do not change appreciably if properly cared for. They should never be left standing in direct sunlight, and should be kept in a box or cupboard when not in use. Even after nine months our standards were in very good condition, the color changes being so slight as to cause practically no error in estimation of the P_H of a urine.

Each standard is prepared to match somewhat closely the color given by 1 c.c. of a Sörensen's phosphate mixture diluted with 20 c.c. of boiled distilled water after the addition of 1 c.c. of indicator, when at ordinary room temperature (15° to 22°). Absolute matching of the colors is not at all necessary. The use of rosolic acid with urine is possible only with the aid of the permanent standards. Sörensen phosphate standards with rosolic acid change color too rapidly for practical use.

For these permanent standards 20 c.c. of the buffer phosphate solution is put into each of the two-ounce square bottles and various amounts of amaranth and paranitrophenol are added as indicated below, and a little preservative (0.2 c.c. 10 per cent thymol in chloroform) is added, then the bottle is corked (but not with a rubber stopper), and sealed with hot paraffin.

PERMANENT STANDARDS AND THE CORRESPONDING SÖRENSEN STANDARDS

PERMANENT STANDARDS			SÖRENSEN STANDARDS		
			PROPORTIONS IN 10 C.C. OF MIXTURE		
P_H	AMARANTH C.C.	PARANITRO-PHENOL C.C.	1/15 MOLAR KH_2PO_4 C.C.	1/15 MOLAR NA_2HPO_4 C.C.	INDICATOR
4.5 (4.49)	1.3	0.2	10.0	0.0	Methyl Red
4.95 (4.94)	1.0	0.45	9.9	0.1	Methyl Red
5.3 (5.29)	0.65	0.75	9.75	0.25	Methyl Red
5.6 (5.59)	0.45	1.1	9.5	0.5	Methyl Red
5.9 (5.91)	0.25	1.0	9.0	1.0	Methyl Red
5.9 (5.91)	0.55	1.0	9.0	1.0	Rosolic Acid
6.25 (6.24)	0.7	0.9	8.0	2.0	Rosolic Acid
6.45 (6.47)	0.9	0.85	7.0	3.0	Rosolic Acid
6.65 (6.64)	1.0	0.65	6.0	4.0	Rosolic Acid
6.8 (6.81)	1.15	0.3	5.0	5.0	Rosolic Acid
7.0 (6.98)	1.3	0.4	4.0	6.0	Rosolic Acid
7.0 (6.98)	0.6	0.45	4.0	6.0	Neutral Red
7.15 (7.17)	0.6	0.65	3.0	7.0	Neutral Red
7.4 (7.38)	0.43	0.6	2.0	8.0	Neutral Red
7.5 (7.48)	0.38	0.65	1.65	8.35	Neutral Red

The exact P_H figures for the Sörensen phosphate mixtures are those given in the parentheses. The approximate figures can be used for most work, since it is impossible to detect differences between solutions that vary by less than 0.05 in their P_H figures.

The concentrations of amaranth and indicator solutions* are as follows:

Amaranth (amaranth No. 107, secured from Eimer and Amend) 8 mg. dissolved in 100 c.c. of distilled water to which is added 0.5 c.c. of the thymol-chloroform preservative.

Paranitrophenol, (furnished by Eimer and Amend) 20 mg. dissolved in 10 c.c. of alcohol and diluted with 90 c.c. of distilled water.

Methyl red (Kahlbaum's) very finely powdered, 2.4 mg. dissolved in 100 c.c. of 60 per cent alcohol.

Rosolic acid (Merck's) powdered, 16 mg. dissolved in 100 c.c. of 95 per cent alcohol.

*Hynson, Westcott and Dunning, Baltimore, have agreed to supply a partial or complete equipment for carrying out the method as described in this paper. The indicators and other chemicals will be supplied in weighed portions ready to be dissolved, so that those who do not have access to a fine balance will not be prevented from using the method. The samples of indicators purchased from certain other dealers were found by the author to be worthless or weaker in indicator value than Kahlbaum's, Merck's and Grübler's preparations.

Neutral red (Grübler's "zu Injekt. i. vital. Gew. nach Ehrlich") finely powdered, 3.2 mg. dissolved in 100 c.c. of 50 per cent alcohol.

For these solutions the concentrations of alcohol need not be exact.

All the solutions should be kept in pyrex or nonsol flasks. The last three indicator solutions must be protected from the light, preferably by painting the flasks black. These indicator solutions can still be used satisfactorily when two months old, although the rosolic acid weakens slightly in that time. After nine months all the solutions had changed so that they were inferior to freshly prepared solutions. In that length of time the rosolic acid became so much weaker that it required the use of 1.3 c.c. instead of 1 c.c. The methyl red and neutral red did not fade appreciably, but the character of the colors given by them was somewhat different as compared with the colors given by fresh solutions. New solutions might be prepared once in two or three months.

TECHNIC OF ESTIMATING THE P_H OF URINE

All glassware used, (bottles, pipettes, flasks, etc.) must be thoroughly washed, rinsed with distilled water, and then tested with a practically neutral indicator solution, (e. g., 20 c.c. distilled water, 1 drop of the buffer phosphate solution and 1 c.c. of rosolic acid). If the test solution becomes less red, contaminating acid is present, if it becomes redder, alkali is present; in either case wash the apparatus and test again. Rinse out the traces of indicator solution with distilled water and proceed with the estimation.

First make a preliminary determination as follows: to 20 c.c. of distilled water in a two-ounce square bottle add 1 c.c. of rosolic acid solution, and immediately add the urine 0.2 c.c. at a time comparing with the rosolic acid permanent standards after each addition until either the P_H determination remains constant or the urinary pigment changes the character of the color. Never use more than 1 c.c. of urine. In the case of highly colored concentrated urine 0.2 or 0.4 c.c. will suffice. This test indicates the amount to use in the final test, i. e., less than will give the disturbing pigment effect but still enough to give the full P_H estimation.

The test also shows which indicator must be used. If the mixture is as yellow as the 5.9 rosolic standard or more yellowish, use methyl red. If it is as red as the 7 rosolic standard or of a deeper red color, use neutral red. If the color is intermediate between that of the 5.9 and 7 standards, use rosolic acid.

For the final test add to 20 c.c. of distilled water the amount of urine determinated by the first test, and last of all 1 c.c. of the proper indicator. Compare with the standards *immediately* (because contamination with CO_2 occurs so easily, and in the case of rosolic acid the color fades rapidly). Avoid getting expired air into the bottle.

It is self-evident that one must be careful to compare the urine mixture only with those standards that correspond to the particular indicator used (for instance, after using rosolic acid for the urine do not match up with the colors given by methyl red or neutral red). It is advisable to have each standard bottle labeled with the indicator, e. g., Methyl R. 5.3, Ros. 6.8, Neutral R. 7.4; thus accidental slips will be avoided.

The P_H figure of the permanent standard that most nearly matches in color the urine test solution is reported as the P_H of the urine. One may guess P_H readings intermediate between the standards although such interpolation is an unnecessary refinement.

We have found that the most accurate and most rapid estimations are made by placing the standard bottle and the urine bottle for comparison against a background of dull white paper with the light (diffused daylight or the special electric light referred to above) passing over the shoulder.

Very little time is required for making estimations.

REMARKS AND EXPLANATIONS

1. In the above discussion it has been taken for granted that the reader understands what is meant by the P_H. For fear that some may not recall it, I shall explain briefly. The P_H figures are the (negative) logarithms of the true hydrogen-ion concentration. For example, a neutral solution is a 0.0000001 normal solution of hydrogen ions; the logarithm of this decimal fraction is −7.0, therefore, the P_H is 7.0 (the minus sign is ignored). The smaller the figure the greater the acidity.

Urine is seldom more acid than 4.5, nor more alkaline than 7.5 (except when sodium bicarbonate, citrate or similar drugs are taken).

2. Toluol is to be added to the urine as a preservative when collecting a 24-hour sample or when the urine can not be examined within an hour after being passed. The urine must not be treated in any other way, not even filtered. If it is turbid it may be centrifuged.

3. Urines containing hemoglobin, bile or great excess of pigment may be dialyzed in a collodion sac against neutral 1 per cent NaCl solution for thirty minutes, as in Rowntree's[6] method for P_H of blood. The P_H of the salt solution is then determined in the same manner as urine.

4. The room must be free of fumes of NH_3, HCl or HNO_3 when estimations are made. Excess of CO_2 (from flames) should be avoided.

5. For measuring amaranth and paranitrophenol solutions and also the urine, 1 c.c. pipettes marked in 0.01 c.c. are needed.

6. When the temperature of the room is above 22° an error may be made in estimation due to the temperature (the permanent standards do not change perceptibly), for instance, if the urine test mixture is at 30° the P_H figure will be greater (more alkaline) than at 20° by about 0.05 (in the case of a distinctly acid urine) up to even 0.20 (in the case of an alkaline urine). This can be obviated readily by cooling the distilled water to about 15° before using it.

7. The presence of protein in the urine does not interfere with the use of any of the indicators.

8. The phosphates for preparation of the buffer solution must be pure. I used Baker's C. P. KH_2PO_4 and Merck's pure K_2HPO_4. The buffer solution must have a P_H of 6.8 when estimated by the same dilution method as in the case of urine.

Dissolve each phosphate separately in about 200 c.c. of distilled water taking 6.808 gm. of powdered KH_2PO_4 and 8.712 gm. of powdered K_2HPO_4.

Mix the solutions and dilute to exactly 500 c.c.; saturate with chloroform and filter. Keep the solution in a pyrex or nonsol flask, tightly corked.

9. A slight precipitate may appear after a time in the permanent standards, but this need not interfere with their use if they are not shaken up.

10. Test the indicator solution at least once a month by making P_H estimations with Sörensen's phosphate mixtures (1 c.c. diluted as in estimating urine), using for methyl red the P_H 5.3 mixture and for neutral red the P_H 7.15 mixture. For rosolic acid the buffer phosphate mixture can be used (P_H 6.8). This procedure also assures one that the permanent standards have not changed enough to cause inaccurate P_H estimations.

11. The distilled water may be tested at any time by adding to 20 c.c. two drops of the buffer phosphate solution and 1 c.c. of rosolic acid, the color must be redder than the 6.65 standard but not redder than the 6.8 standard. The distilled water should not be too old.

SUGGESTION OF A NEW WAY OF EXPRESSING ACIDITY OF THE URINE FOR CLINICAL PURPOSES

Many persons do not readily grasp the idea of the P_H notation and quickly forget the explanation. It is also confusing to many that the P_H figure should become smaller as the acidity increases.

In devising a new notation advantage may be taken of the proportion of acid phosphate (KH_2PO_4) in the Sörensen standards. For instance, a phosphate standard having a P_H of 6.8 is a 50:50 mixture of the two phosphate solutions, and contains an equal number of molecules of each phosphate in 1 c.c. of solution. Its acidity may therefore, be called 50 (not 50 per cent). The P_H 4.5 phosphate standard contains only the acid phosphate and would be assigned an acidity of 100. The full notation would be as follows:

PH	CLINICAL ACIDITY FIGURE	PH	CLINICAL ACIDITY FIGURE
4.5	100	6.65	60
4.95	99	6.8	50
5.3	97.5	7.0	40
5.6	95	7.15	30
5.9	90	7.4	20
6.25	80	7.5	16.5
6.45	70		

The use of the expression *per cent* should be avoided because per cent refers to the proportion of substance by weight. Sörensen's alkaline phosphate solution is a 1.187 per cent solution, and the acid phosphate is a 0.907 per cent solution. The percentage of the total phosphate present as KH_2PO_4 in a phosphate solution of acidity 80 (P_H 6.25) is actually 75 per cent. Also the acidity figures do not indicate the relative concentration of hydrogen ions present in solution, for example, a Sörensen phosphate solution of P_H 4.95 contains about 100 times as many H ions per cubic centimeter as a phosphate solution of P_H 7.0, but the relation of the acidity figures is 99:40.

Although it is true that the acidity figure indicates the percentage of the total number of phosphate molecules that are present in a solution as KH_2PO_4 molecules, *it is advisable to refrain from using the term per cent.*

SUMMARY

Modifications of the somewhat difficult standard method are proposed which should enable the physician to estimate with ease and with considerable accuracy the true acidity of the urine. A new notation for the various degrees of acidity is also suggested that may make the method easier for clinicians.

BIBLIOGRAPHY

[1]Henderson, L. J., and Palmer: Jour. Biol. Chem., 1913, xiii, 393.
[2]Sellards, A. W.: Bull. Johns Hopkins Hosp., 1912, xxiii, 289.
Palmer, W. W., and Henderson, L. J.: Arch. Int. Med., 1913, xii, 153.
[3]Palmer, W. W., and Van Slyke, D.D.: Jour. Biol. Chem., 1917, xxxii, 499.
[4]Palmer, W. W., and Henderson, L. J.: Arch. Int. Med., 1913, xii, 160.
[6]Rowntree, L. G. (and others): Arch. Int. Med., 1915, xvi, 389.

A COMBINED MEASURING AND INJECTING PIPETTE*

By George B. Roth, Washington, D. C.

IN order to conform to the U.S.P. method for the physiologic assay of the members of the digitalis series it is necessary to use small amounts of the modified drugs. The transfer of small amounts of fluid from a measuring pipette to a glass container and then to an injecting pipette introduces a slight error which can be avoided by the use of the following described pipette. The combined pipette serves not only for the measuring of the drugs, but for their injection as well. Its use prevents the loss of fluid and shortens the time required for making a series of injections.

The pipette is made from the barrel of an all-glass tuberculin syringe or preferably from a short glass delivery pipette which has a capacity of 1 mil. and which is graduated to 100ths of a mill. (See *A* in illustration.) The lower end of the syringe, or pipette, is drawn out into a fine point similar to an injecting pipette with the exception that the extreme point is closed and pointed sharply. Near the closed pointed end is a small opening. (See *B* in illustration.) The closed point being sharp permits of the easy entrance of the pipette into the anterior lymph sac of the frog while the position of the lower opening of the pipette, being above the extreme point, prevents the opening from being clogged with tissue when the lymph sac is entered. Gravity is sufficient for the injection of the fluid so that the amount introduced can be carefully controlled by admitting air into the upper opening of the pipette.

*From the Hygienic Laboratory, U. S. Public Health Service.

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Editor-in-Chief: VICTOR C. VAUGHAN, M.D.
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EDITORIALS

Medical Education in Great Britain

MEDICAL education in Great Britain does not differ widely from that of this country. The minimum requirement is university matriculation which is practically the same as ours of graduation from a first-class high school. The medical course in the British medical schools covers a minimum of five years, but one year of this time is given to chemistry, physics and biology which are included in our premedical course. In fact, one year of credit is given in British medical schools to those who have already passed in these subjects. In the British medical schools Latin is no longer an essential requirement. It will be seen from the above statements that the requirements for admission to the British medical schools are equivalent with us to graduation from a high school with the addition of one year of collegiate work in physics, chemistry and biology. Our Standard Class A medical schools are in advance of the British medical schools so far as admission requirements are concerned.

In the British medical schools the course is divided into the following three groups:

(a) Preliminary Science
(b) Intermediate,
(c) The Final.

The first corresponds to our premedical work, but demands only one year in time. The second is given wholly to anatomy and physiology, and covers two years of work. (It may be remarked that this is an indication of why English medicine has held a predominant rank in anatomy and physiology.) In the third period British medical students have bacteriology, pathology and all the clinical branches and two years of time are given to this period.

Our British colleagues stress examinations much more than we do, and since these are held only at fixed times there is often much delay in the progress of the individual, and six and even seven years may be given to the medical course, and often are, by the average medical student. In some schools students are permitted to take examinations on the completion of each of the three above-named groups. In other schools no examination is held until the completion of all the course. The average cost to the student of his medical course is about five thousand dollars.

The *British Medical Journal* (August 31, 1918) has the following to say concerning the effect of the war on the number of medical students: "Between the years 1910-14 the annual entry of first year medical students averaged roughly 1,440. Since the war the number of these entries has increased by five or six hundred a year. Thus, the whole number of students actually pursuing medical studies in the schools of the United Kingdom has shown an upward steady movement. In May 1916 the total was 6,103; in June 1917 it was 6,682; in October 1917 it was 7,048; while the latest figure for May 1918 was 7,630. But for some time the large withdrawls of male students from medical schools for combatant service, or as surgeon probationers in the navy, more than nullified the increased entries, and bade fair to produce a serious deficiency of new probationers in the years 1918-1919. Urgent representations upon this matter were made to the Government; as a result something has been done to make good the threatened shortage by the return of third year students from active service to complete their studies, by the retention in the medical schools of students on their way to qualifications who are liable to be called to the colors, and by limiting the period of service of surgeon probationers. The Minister of National Service has further undertaken to provide that, if possible, the supply of students in training shall be kept at a level sufficient to give an annual yield of at least 1,000 practitioners."

The number of female medical students has greatly increased and stands now at about 2,250. It seems from the above that the probabilities are when this war closes the number of medical practitioners in Great Britain will be sufficient to supply the demand.

The full effect of the national insurance put into operation before the war on the profession can not be yet determined. It has certainly greatly reduced

the incomes of many of the more expert practitioners, and has increased that of the less efficient. It is impossible to predict the state in which the profession will find itself when the war ends. It is possible, and indeed highly probable, that the socialization of the profession will be greatly advanced. Whether this will be for the good of the profession, or for the good of the people, or for the good of both, will depend upon the lines upon which the advance is made. Great wisdom is needed to direct this procedure.

Most of the universities in Great Britain give courses and degrees in public health. These courses are open only to those who are qualified to practice medicine. They can not be shorter than nine calendar months, and include four months of laboratory work in which chemistry, bacteriology and the pathology of diseases of animals transmissible to man are taught. Six months are given to the questions of health administration and attendance at least twice weekly for three months at a hospital for infectious diseases. While Public Health Service falls far short of perfection, it must be admitted that, judged by the results, it is the best in Europe. There is no other European country in which infections are so well controlled and the death rate so low. This training in public health has been of the greatest service during the present war, both in the civilian and the military population. The service is not uniform, and much is left to local initiative. Appointments are made by local boards. The medical officer of health in a country borough—a designation which includes nearly all the larger towns—is a permanent appointment. The medical officer to a district of 50,000 or more must hold a diploma in public health. School medical inspectors are appointed by the local school boards. The function of the school inspector is broader than it is with us. He must not only watch for infectious diseases, but for physical and mental defects which he must report to the parents and aid them in securing remedies. Not infrequently the office of health supervisor and that of school inspector is held by the same individual. These duties may be shared by an assistant. Under the Insurance Act tuberculosis officers take charge of dispensaries devoted to this disease. These are whole time officials who have special training and the salary is $2,500.

A large proportion of medical practitioners in Great Britain do not possess the degree M.D. In fact, the matter of medical degrees and the number and variety of bodies conferring such degrees is too complicated and too uninteresting to us in this country to justify the time, energy or space necessary to learn it. In our College of Surgeons we are imitating our British confreres. Whether this move is a wise one or not, someone else may discuss.

—*V. C. V.*

Transmission of Influenza

DESPITE the quite tremendous amount of work that has been done in attempting to clarify and elucidate the etiologic problems connected with influenza, very little of practical importance has been evolved. The virus is still

uncertain, if not indeed unknown. Suspicion implicates, depending largely upon the results of bacteriologic work, both B. influenzae (Pfeiffer) and the pneumococci. Also, depending upon the unproductiveness of bacteriologic labors, and of experimental work, certain workers hold to the conception that an unknown filterable virus is the probable essential cause of the complex.

Influenza undoubtedly belongs to the group of diseases which have come to be called "respiratory." It seems surely to be, so far as we can judge, a "spray-borne" disease, by which is meant that the virus is transmitted by spray, resulting from coughing and sneezing, from the respiratory tract of one individual to that of another. There seems to be good evidence also that it may be carried on the hands, and even by dishes, as well as by handkerchiefs and towels. Judging from the rate of spread from person to person the infectious agent is of considerable pathogenicity. Despite all these facts no one seems to have been able to isolate the virus, and only in a few instances has experimental work indicated the definite presence of the virus in the respiratory secretions.

In October 1918, Nicolle and Lebailly concluded from their experiments that the bronchial expectoration of influenza patients is virulent for human beings and for monkeys. These writers used the material from a patient who had been ill two days for inoculations. Filtered and unfiltered specimens were used. The unfiltered substances were inoculated into monkeys by the subjunctival and nasal routes, and in each case caused the disease. The filtered material was used upon human volunteers to whom it was given subcutaneously and intravenously. Those inoculated subcutaneously contracted the disease; those inoculated intravenously did not. Blood taken from a monkey suffering from the disease and introduced subcutaneously in humans did not produce the disease. From these experiments it is concluded that the cause of the disease is a filterable virus which does not inhabit the blood stream, but which does inhabit the respiratory tract.* These early experiments were carried out in an exceedingly small scale.

Following the French investigation, have come the ones carried out under the auspices of the United States Public Health Service and the United States Navy. These have been carried out in two parallel series, one at Boston, Mass., and one at San Francisco. At each, the same methods were used, and consisted in inoculations of human volunteers with pure cultures of Pfeiffer's bacillus, with secretions from the upper air passages, and with blood from typical cases of influenza.†

The studies were begun with an experiment in which a suspension of a freshly isolated culture of Pfeiffer's bacillus was instilled into the nose of each of three nonimmunes and into the nose of each of three immunes. None of the subjects showed any reaction after the treatment. Another experiment was made at a later date with a suspension of a number of pure cultures of the bacillus. Ten nonimmune volunteers were inoculated with negative results. Three sets of experiments were made with secretions,—both filtered and unfiltered,—from the upper respiratory tract of typical cases of influenza in the most active stage of

*Compt. rend. Acad. d. sc., 1918, clxvii, 607.
†Public Health Reports, 1919, xxxiv, 33.

the disease. In these experiments a total of 30 men were subjected to inoculation by means of sprays, swabs, or both, of the nose and throat. The interval elapsing between securing secretions from the donors and inoculation of the volunteers was progressively reduced in these experiments so that in the third of the series the interval at most was 30 seconds. In no instance was an attack of influenza produced in any one of the subjects. An experiment was made in which the members of one of the groups of volunteers which had been subjected to inoculation with secretions were exposed to a group of cases of influenza in the active stage of the disease in a manner intended to stimulate conditions which in nature are supposed to favor the transmission of the disease. Each of this group of ten volunteers came into close association for a few minutes with each of ten selected cases of influenza in the wards of the Chelsea Naval Hospital. At the time the volunteers were exposed to this infection the cases were from ten to eighty-four hours from the onset of their illness and four of them were not twenty-four hours after the onset. Each volunteer conversed a few minutes with each of the selected patients, who were requested to, and coughed into the face of each volunteer in turn, so that each volunteer was exposed in this manner to all ten cases. The total exposure amounted to about three-quarters of an hour for each volunteer. None of these volunteers developed any symptoms of influenza following this experiment.

Advantage was taken of the opportunity for making this study to attempt to confirm the reported positive results of transmission of influenza by Nicolle. Secretions from five typical cases of influenza were secured, filtered, and some of the filtrate was inoculated subcutaneously into each of the group of ten volunteers. At the same time blood was drawn from the same cases and pooled, and some of the mixed blood injected subcutaneously into each of another group of ten volunteers. The time lost between drawing the blood and inoculating it in no case exceeded three-quarters of an hour. None of the men subjected to these inoculations developed any evidences of illness.

The San Francisco observations were made practically simultaneously with those described above. In the parallel series the volunteers who were used differed from those used at Boston in two respects—first, the personnel of the Yerba Buena Station had not been exposed to influenza in the present epidemic and were therefore presumed not to possess any special natural immunity; second, all of the men had been vaccinated with large doses of a bacterial vaccine containing Pfeiffer's bacilli, the three fixed types of pneumococci and hemolytic streptococci. We are not prepared at present to state what influence this vaccination may have had in promoting resistance to influenza infection, but if we may judge by the results of controlled experiments elsewhere such vaccination may for the present purpose be ignored. One group had instilled into the nostrils of each man a heavy suspension made by emulsifying cultures of eight strains of Pfeiffer's bacillus without filtration. The other group had the same material used after passage through a Berkefeld N candle. The results were negative, though the men were held under observation for seven days.

Emulsions of secretions from the upper respiratory passages of active cases of influenza from 15 to 48 hours from the onset were instilled into the nose by

means of a medicine dropper or with an atomizer. In each experiment approximately an equal number of volunteers were treated with the same emulsion after filtration through a Berkefeld N candle. In every case the results were negative, so far as the reproduction of influenza is concerned. The men were all observed for seven days after inoculation.

A filtered emulsion of material from the upper air passages of an acute case of influenza was dropped into the conjunctivæ of two volunteers and the same material injected subcutaneously into one volunteer. In each case the result was negative.

One cubic centimeter of blood taken during the active stage of influenza was inoculated subcutaneously into one volunteer with negative results.

Judging from these three important pieces of experimental work one would say that influenza was transmitted with a very considerable degree of difficulty, and yet the facts observed during the epidemic indicate that the reverse is true. One may reasonably suspect that there are essential conditions, especially in the American series, which inhibited transmission. The positive results of the French investigators overbalance the negative ones of the American. To arrive at certain results further work must be done with subjects who are certainly nonimmune. Before that can be done some method of determining immunity must be devised.

—*P. G. W.*

Hand to Mouth Infection

WE have long recognized the fact that the hand of all the members of the body is most frequently the bearer of infection. Long before we knew anything about bacteria it was the custom of decent people to wash their hands before eating. The most ignorant mother sends her little boy from the table when he comes with dirty hands, and tells him that it is not necessary for him to eat the proverbial peck of dirt. The surgeon has spent much time in investigating the methods necessary to so thoroughly cleanse his hands that they may not serve to carry infection to the wounds upon which he operates. He found that sterilization of the hands was difficult and so uncertain that he resorted to the use of rubber gloves. It is true that bacteria may be carried without harm into the mouth which would endanger life if introduced into the wounds; however, that the hand often serves to carry harmful organisms to the mouth and to the respiratory organs is conceded by all.

In army life the soldier is instructed to wash his hands before eating and after visiting the toilet. When one has watched the soldier, the average soldier complying with this order, he recognizes how unsatisfactorily it is done. Possible methods for securing more perfect cleanliness of the hands among soldiers have been the subject of serious and prolonged discussion among medical officers. The same is true concerning the cleaning and sterilization of mess kits. Order after order has been issued concerning this matter, and still, however observant, the medical officer is well aware of the unsatisfactory results obtained.

Recently Col. Lynch and Lieut.-Col. Cumming have called attention to this matter from a somewhat different standpoint than has been done at any previous

time. These officers have shown by statistics that the respiratory diseases are less prevalent among soldiers who use table ware than among those who use mess kits. The usual method of cleaning the individual mess kit is as follows:

A garbage can is filled with hot water, boiling water to start with, in which soap is dissolved. The volume of the contents of the can is subject to considerable variation, but is limited at most to a few gallons. In this two hundred and fifty mess kits are sometimes washed. The water, boiling at first, rapidly lowers in temperature, and soon reaches that of the optimum growth of bacteria. Each soldier puts his hand in the water and scrubs his mess kit. Lieut.-Col. Cumming has made a study of the bacteria in the wash water. In the first place he finds that the number of bacteria removed from the hands depends upon the temperature of the water, that in water from 38° to 50° the number of bacteria removed from the hand and consequently distributed in the wash water is larger than at lower or higher temperatures. He has shown that by the time the Company mess kits have been washed in one of these cans, the fluid has become a rich culture and may contain more than one hundren thousand bacteria per cubic centimeter. Every soldier's hands have been immersed in this fluid. After scrubbing his mess kit in the soapy solution, the soldier dips his mess kit, or is supposed to, in boiling water. This is not always done, but granting that it is done and that that portion of the kit which is immersed in the boiling water is sterilized, what is the condition of the hands which have been immersed in the bacterial culture? This is really more important than the sterilization of the mess kit. The soldier with his hands moist with this fluid rich in bacteria, puts his hands to his mouth, picks his teeth with his fingers, holds the fruit which he eats, hands food to his comrades, opens doors, infecting the knob, spreads the infection over his clothing, and distributes to others the various bacteria present in the wash water. Some of these bacteria he may carry under his nails for days.

The main point brought out by Col. Lynch and Lieut.-Col. Cumming is the infection of the soldier's hands in washing his mess kit. This is of more importance than the failure to sterilize the kit.

There are other ways in which our hands become the bearers of infection. We blow our noses into our handkerchiefs, handle the handkerchief both while it is still moist and after it is dry, then shake hands with our best friends, transferring bacteria along with the greeting.

The story is told of a wicked woman who wore a ring in which there was a spring which moved a fine sharp lancet. When she affectionately and tenderly grasped the hand of her dearest friend she pressed the spring and inoculated her friend with a deadly poison. This is probably all fiction; but how many have been inoculated by the handshake of a friend, no one can tell.

There are various ways in which mess kits can be sterilized. This is a comparatively easy problem; but how to keep the hand free from pathogenic germs at all times is a wholly different and much more difficult proposition.

Workers in bacteriologic laboratories are in the habit of washing their hands in various disinfecting agents. Some use a 10 per cent solution of crude lysol. This is not an unpleasant application, and when allowed to remain upon

the hands for some moments and then washed off with sterile or even safe tap water seems to be efficacious. Probably the most common constituent of the sterilizing jar for washing the hands in the bacteriologic laboratory is a solution of mercuric chloride, one to one thousand. However, this is not efficient. The mercuric chloride coagulates protein substances, and in the coagulent, germs may be entangled and protected from the action of the disinfectant. For this reason the solution of mercuric chloride is not to be recommended. In other laboratories a 5 per cent solution of carbolic acid is used. This is not so agreeable an application as the 10 per cent solution of lysol and probably not so efficient. In still other laboratories the jar for washing the hands contains a saturated aqueous solution of chlorine gas. In my opinion this is the most satisfactory agent for the sterilization of the hands. Of course the chlorine must be washed off the hands with water. Since chlorine is used in almost every camp in the sterilization of water, it might be possible to provide a solution of this kind in which soldiers could wash their hands.

At any rate we must admit that the possibilities of hand to mouth infection are great, and some provision should be made whereby the ill effects may be reduced to a minimum.

—*V. C. V.*

The Toxin of Bacillus Influenzae

THERE are two features of the disease influenza which point to its being due to the action of a powerful toxin, one is the consistent leucopenia,—the other is the rapidity of its onset and extreme prostration. Since there is no certainty regarding the bacterial cause of the disease a search for a toxin must be based upon purely empiric grounds. Since B. influenzæ is under suspicion, and since comparatively little is known of the biologic activities of this organism certain recent studies have centered about it. Most interesting of such studies is that recently published by Julia Parker* on toxin production. Her results are astonishing, and indicate that the organism produces a substance of great toxicity under the conditions of the experiments, i. e., after growth on veal infusion media. "The poison is produced with remarkable speed. We have obtained very toxic filtrates even after only from six to eight hours' incubation. At this time the organisms are growing very rapidly. Most of our work has been done, however, with eighteen or twenty hours' growth. There is no relation between the amount of growth and poison formation. After incubation the cultures were centrifugalized, and the supernatant fluid was filtered through a Berkefeld candle. The sterile filtrate was then inoculated intravenously into rabbits. The poison deteriorates very quickly, even when kept in the ice box. For this reason the toxicity of the poison must be tested, and the experiments made on the same day. If 2 c.c. of a poison killed a medium sized rabbit in from one to three hours, we considered it a good poison. Sometimes rabbits died when injected with 1 c.c. of a poison, but this was not the usual result. When

*Jour. Am. Med. Assn., 1919, lxxii, 476.

a rabbit is given a lethal dose of the poison, there is an incubation period of about thirty minutes before any symptoms appear. This is followed by increasing weakness, often accompanied by diarrhea. Death usually occurs within three hours, with or without convulsions. Immunologic tests were carried out as follows: Rabbits were immunized to multiple lethal doses of the poison. The serum of rabbits that have withstood at least four lethal doses of the poison will protect normal animals against lethal inoculation of the poison. An immunity against a poison produced from any one strain will protect against a poison from any other strain. This protection is shown in two different ways:

"A. By mixing the lethal dose of the poison *in vitro* with the serum before inoculation.

"B. By giving the serum fifteen minutes before or fifteen minutes after the injection of the poison."

These experimental results may be used in explanation of many of the clinical facts of the disease, and also of the discrepancies which appear in the human experimental work in connection with influenza.

—*P. G. W.*

The Human Tubercle Bacillus—Are There Distinct Types?

BROWNLEE,* who has a reputation among his colleagues as "being very learned and more capable of extracting truth from statistics than is any one else in England," has suggested from statistical analysis of the Registrar-General's returns of mortality from phthisis that we may possibly be dealing with three types of the human tubercle bacillus.

As is pointed out in an introduction by the Medical Health Committee of the National Health Insurance to "An Investigation Into the Epidemiology of Phthisis in Great Britain and Ireland," by Dr. John Brownlee, the knowledge of types of pneumococcus, dysentery, typhoid, meningococcus and possibly tetanus, would lead to a suggestion that there might be separate types of the tubercle bacillus causing phthisis. What is novel is "that the detection of distinct types should come sooner from statistical than from bacteriological analysis." Brownlee's studies and charts suggest that we may be dealing with three types of the human tubercle bacillus.

1. The "young adult" type. Death resulting between 20-25 years.
2. The "middle age" type. Death resulting between 45-50 years.
3. The "old age" type. Death resulting between 55-65 years.

These types are shown to have different geographical distribution in Great Britain. Charts are given showing for instance that in the Shetland Islands only the "young adult" type exists, whereas in London practically only the "middle age" type exists.

The statistics of the Registrars-General of England, Scotland and Ireland which are analyzed cover a period of over fifty years, and it is probably rightly claimed that these statistics can be matched by no other country.

*An Investigation into the Epidemiology of Phthisis in Great Britain and Ireland. National Health Insurance, His Majesty's Stationery Office, London.

Inasmuch as populations of certain sections and cities are found to vary in age constitution, a ratio is given between the number of deaths from phthisis and the number of persons living at the same age period, this death rate being expressed in parts per thousand or per million.

The diagrams show that a great diminution in the mortality of phthisis has occurred in the last fifty years, but that this decrease is unequally distributed over the different ages.

A most conspicuous fall in the death rate is noted at the ages twenty to twenty-five, and this in spite of the disease at this age period being the easiest of all to diagnose.

The curves embracing the whole of Great Britain have been generally known. The analysis of returns from limited areas have not heretofore been plotted, and it is a study of these that has led Brownlee to suspect the possibility of the different types.

Data from every county in England were investigated and in this manner the striking age distributions were found. The "young adult" type was generally noted throughout England and Wales with the exception of Lancashire, part of Yorkshire, Staffordshire, Warwickshire and London. In these regions the type of "middle age" phthisis was especially high. It was not possible to analyze Ireland by counties but as a whole it shows a preponderance of the "young adult" type.

Mortality curves contrasting North Wales and London are most striking. They serve to convince one that combined mortality curves of England and Wales would have masked important observations and deductions. In North Wales for the period of 1861 to 1870 the "young adult" type registered nearly 7000 deaths per million living at that age, rapidly declining to 4000 per million in middle age. The 1891 to 1900 period also shows a rapid rise to the "young adult" type, but only registering 2700 per million and the record remaining almost horizontal until sixty-five years. In London, on the other hand, the curve rises to a maximum in both the periods 1861-1870 and 1901-1910 between the ages of forty-five to fifty-five years, 6500 per million for the former and 4500 per million for the latter. The "young adult" type is remarkably slight in amount being 4000 per million in the former and only 1700 per million in the latter.

In general Brownlee notes that the chief seats for the early phthisis are in seaboard and agricultural counties, so much so that in the Shetland Islands there is almost no phthisis at all except this "young adult" type. He suggests, therefore, that Hippocrates may not have been incorrect in his statement that the chief ages of the susceptibility to phthisis were between 15 and 35 years. This would seem to be true today in Wales, a country comparable to Greece.

Cornwall would seem to be a county especially conspicuous for the "old age" type, and it is shown that this has nothing to do with the tin mining industry inasmuch as the incidence is the same in the population not engaged in this work.

It is noted that in Northampton and Leicester, the chief seats of the boot and shoe manufacture, early phthisis is frequent; consequently there is a con-

siderable amount of early phthisis among the boot and shoe makers. It is pointed out that the incidence of pulmonary tuberculosis in different trades must be compared with the incidence and type in the immediate neighborhood and not with that at large.

There is found to be three times as much "old age" phthisis among males as among females, and in females the "young adult" type is a little later than among males, and the "middle age" type a little earlier than among males.

The effect of environment is considered and the following results are suggested: phthisis of the "middle age" type is an infection of which the virulence is increased by the presence of unhealthy conditions, but phthisis of the youth and "old age" types is infection of which the spread is not affected by such conditions.

The idea that an infectious disease is not necessarily more abundant where there is more overcrowding is instanced in regard to scarlet fever. Figures on scarlet fever have been published showing that as room density increases the amount of scarlet fever decreases and that in the best parts of the city of Glasgow there is nearly three times as much scarlet fever as in the worst. When spread by milk, however, notoriously the opposite is found.

It is estimated that a small positive correlation found between the "young adult" and "old age" types indicates that a small number of people can become infected by the tubercle bacillus in youth, hold it at bay during the years of manhood, but succumb to the infection in old age, but most of the cases of "old age" tuberculosis must be regarded as new.

So far only Parts I and II of Brownlee's studies have been published and further publications will be awaited with interest. Should bacteriologic studies confirm his suggestions, practical results may be expected, as he suggests in the more specific tuberculins which may be prepared for each type.

The evidence produced indicates that the epidemiology of the two chief types of phthisis, namely, the "young adult" and "middle age" types, is different. The present epidemic of phthisis of the former type had its maximum about the middle of the last century, while the epidemic of phthisis among the middle aged had its maximum fully one hundred years ago.

The increase in the mean age at death from phthisis which has been steadily rising and which has been explained as due to more immunity and better hygienic conditions of the population would also be possible of explanation by the disappearance of the "young adult" type of disease.

Brownlee's contributions are both stimulating and refreshing and they will certainly give an impetus to laboratory and statistical studies in America.

The great reduction noted in the serious pulmonary tuberculosis at the age of twenty-five would serve to indicate that in our army so largely composed of young men we at present may not expect a large incidence of men returned from France with this disease.

—*G. B. W.*